

THE LANCET Microbe

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

Supplement to: Bosaeed M, Balkhy HH, Almaziad S, et al. Safety and immunogenicity of ChAdOx1 MERS vaccine candidate in healthy Middle Eastern adults (MERS002): an open-label, non-randomised, dose-escalation, phase 1b trial. *Lancet Microbe* 2021; published online Nov 3. [https://doi.org/10.1016/S2666-5247\(21\)00193-2](https://doi.org/10.1016/S2666-5247(21)00193-2).

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Supplementary Table 1. Unsolicited adverse events considered possibly, probably or definitely related.

Subject ID	Symptoms	MedDRA code	Time point (Day#)	Duration (days)	Max. Severity
MERS002-007	Paresthesia	10033987	4	3	2
MERS002_002	Dizziness	10013573	0	1	1
MERS002_015	Dizziness	10013573	1	1	1
MERS002_032	Sneezing	10041232	0	2	3
MERS002_022	Localized erythema	10024781	1	5	1
MERS002_027	Swelling arm	10042680	1	2	1
MERS002_038	Rhinorrhea	10039101	1	1	1
MERS002_038	Headache	10019211	7	1	1

Supplementary Table 2. Laboratory AEs considered possibly, probably or definitively related.

<i>ID</i>	Group	Gender	Event	Value	Severity	Onset	Resolved	D0	D2	D7	D28
<i>MERS002_026</i>	2	Male	Leukocytosis	11.8	Mild	D7	D28	11.5	10.4	11.8	10.9
<i>MERS002_027</i>	3	Female	Leucopenia	0.89	Mild	D2	D7	1.51	0.89	1.9	1.9
<i>MERS002_027</i>	3	Female	Lymphocytopenia	3.17	Mild	D2	D7	5.74	3.17	5.53	5.11
<i>MERS002_030</i>	3	Male	Neutropenia	0.86	Moderate	D2	D7	2.28	0.86	1.93	1.87
<i>MERS002_030</i>	3	Male	Leucopenia	3.17	Mild	D2	D7	4.61	3.17	4.46	4.03
<i>MERS002_031</i>	2	Male	Neutropenia	1.38	Mild	D2	D28	2.22	1.38	1.42	2.73
<i>MERS002_035</i>	2	Female	Neutropenia	1.12	Mild	D2	D7	1.88	1.12	1.74	1.45

Normal ranges: (WBC: $3.51 - 11.49 \times 10^9/L$), (Neutrophils: $1.5 - 7.5 \times 10^9/L$), (Lymphocytes: $1 - 4.4 \times 10^9/L$).

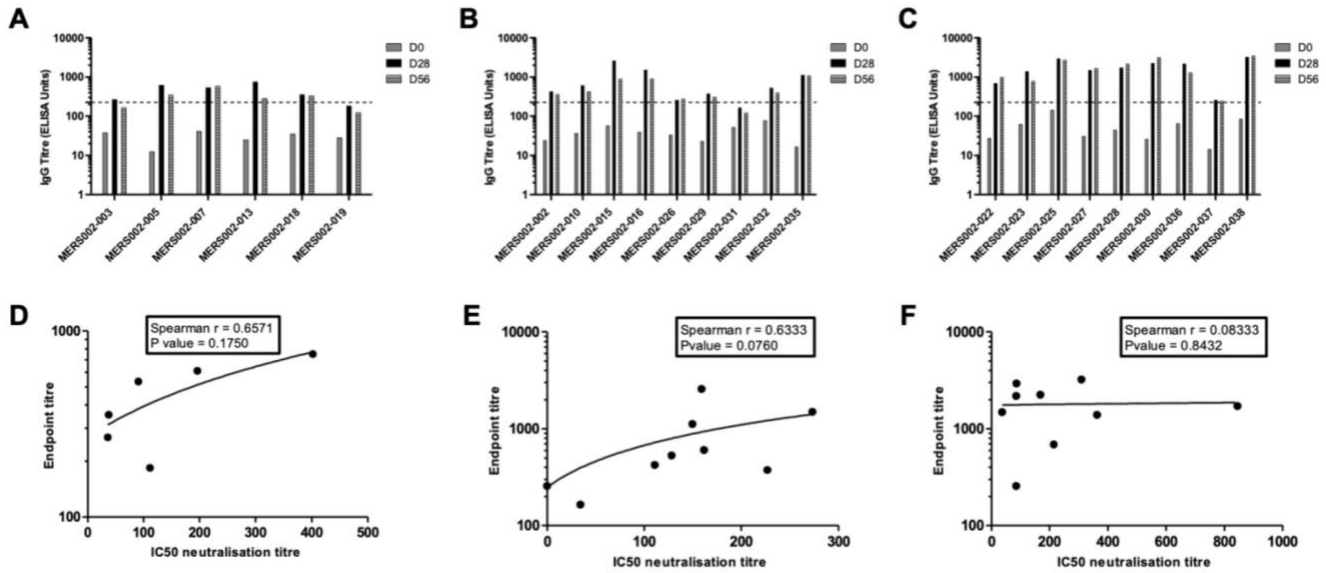
Supplementary table3: List of all solicited Local AEs, with time point and severity*.

	Local Pain							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	MERS002-005	1	1	0	0	0	0	0
	MERS002-003	0	1	1	0	0	0	0
	MERS002_013	0	0	1	0	0	0	0
2	MERS002_010	1	1	1	0	0	0	0
	MERS002_015	0	1	1	1	0	0	0
	MERS002_016	0	1	1	0	0	0	0
	MERS002_026	0	1	0	0	0	0	0
	MERS002_029	0	2	2	2	0	0	0
	MERS002_031	0	1	1	0	0	0	0
	MERS002_032	1	0	0	0	0	0	0
	MERS002_035	0	1	0	0	0	0	0
3	MERS002_025	0	0	1	1	0	0	0
	MERS002_027	0	1	1	0	0	0	0
	MERS002_028	0	1	1	0	0	0	0
	MERS002_037	0	1	0	0	0	0	0
	Warmth							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_002	1	0	0	0	0	0	0
	MERS002_016	0	1	1	0	0	0	0
	MERS002_029	0	2	0	0	0	0	0
3	MERS002_027	0	1	1	0	0	0	0
	MERS002_028	0	1	0	0	0	0	0
	MERS002_036	0	1	0	0	0	0	0
	Itch							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_002	0	1	0	0	0	0	0
Severity grading scale: GRADE 0= None: Symptom not experienced; GRADE 1= Mild: Short-lived or mild symptoms; medication may be required. No limitation to usual activity; GRADE 2 = Moderate: Mild to moderate limitation in usual activity. Medication may be required; GRADE 3 = Severe: Considerable limitation in activity. Medication or medical attention required.								

Supplementary table 4: List of all solicited systemic AEs, with time point and severity*.

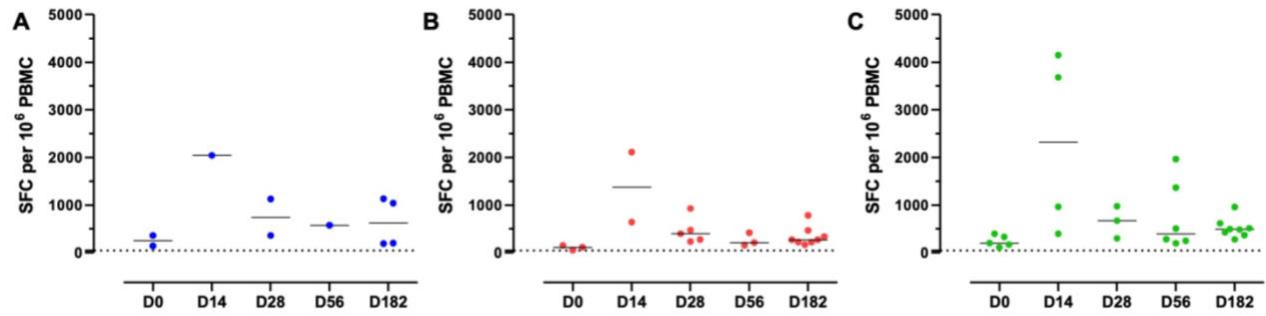
	Temperature							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_002	1	1	0	0	0	0	0
	MERS002_029	0	2	0	0	0	0	0
	MERS002_035	0	1	0	0	0	0	1
3	MERS002_027	0	1	2	0	0	0	0
	MERS002_028	0	2	0	0	0	0	0
	MERS002_036	0	2	0	0	0	0	0
	Feverish							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_016	0	0	0	1	1	0	0
	MERS002_029	0	3	1	0	0	0	0
	MERS002_035	0	3	0	0	0	0	0
3	MERS002_022	1	0	0	0	0	0	0
	MERS002_025	2	1	0	0	0	0	0
	MERS002_027	0	1	1	0	0	0	0
	MERS002_028	0	1	0	0	0	0	0
	MERS002_036	0	1	0	0	0	0	0
	Joint pain							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_010	0	0	0	1	1	1	0
	MERS002_015	1	1	1	0	0	0	0
	MERS002_029	0	2	1	1	0	0	0
	MERS002_035	0	3	0	0	0	0	0
3	MERS002_025	1	1	0	0	0	0	0
	MERS002_037	0	1	0	0	0	0	0
	Muscle pain							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	MERS002-003	0	1	1	0	0	0	0
	MERS002_018	0	1	0	0	0	0	0
2	MERS002_010	1	0	1	0	0	0	0
	MERS002_015	1	1	0	0	0	0	0
	MERS002_016	0	1	1	1	0	0	0
	MERS002_029	0	2	2	1	0	0	0
	MERS002_032	0	0	1	0	0	0	0
	MERS002_035	0	3	0	0	0	0	0
3	MERS002_022	1	1	0	0	0	0	1
	MERS002_025	1	2	1	0	0	0	0
	MERS002_028	0	1	0	0	0	0	0
	MERS002_036	0	1	0	0	0	0	0
	MERS002_038	0	1	1	0	0	0	0

	Fatigue							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_015	1	2	1	0	0	0	0
	MERS002_016	0	1	1	1	1	0	0
	MERS002_029	0	0	2	0	0	0	0
	MERS002_032	2	0	0	1	0	0	1
3	MERS002_025	0	1	0	0	0	0	0
	MERS002_027	0	1	1	0	0	0	0
	MERS002_030	0	1	0	0	0	0	0
	MERS002_036	0	1	0	0	0	0	0
	MERS002_038	0	1	0	0	0	0	0
	Headache							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2	MERS002_002	1	0	0	0	0	0	0
	MERS002_010	0	1	0	0	0	0	0
	MERS002_015	0	0	0	1	0	0	0
	MERS002_016	1	1	1	1	0	0	0
	MERS002_026	0	1	0	0	0	0	0
	MERS002_029	1	3	3	0	0	0	0
	MERS002_031	0	0	0	0	0	1	0
	MERS002_032	1	0	2	2	1	0	1
	MERS002_035	0	3	0	0	0	0	0
3	MERS002_025	1	1	0	1	0	0	0
	MERS002_027	0	1	1	1	0	0	0
	MERS002_028	0	2	0	0	0	0	0
	MERS002_036	0	1	0	0	0	0	0
	MERS002_038	0	1	1	0	0	0	0
	Nausea							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	MERS002_018	1	1	0	0	0	0	0
2	MERS002_010	0	2	0	0	0	0	0
	Malaise							
Group	Volunteer	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	MERS002-005	1	0	0	0	0	0	0
2	MERS002_016	0	1	1	0	0	0	0
	MERS002_029	0	2	2	0	0	0	0
3	MERS002_025	0	1	1	0	0	0	0
	MERS002_027	0	1	1	0	0	0	0
Severity grading scale: GRADE 0= None: Symptom not experienced; GRADE 1= Mild: Short-lived or mild symptoms; medication may be required. No limitation to usual activity; GRADE 2 = Moderate: Mild to moderate limitation in usual activity. Medication may be required; GRADE 3 = Severe: Considerable limitation in activity. Medication or medical attention required. Temperature grading: GRADE 0 = <37.6°C; GRADE 1 = 37.6°C - 38.0°C; GRADE 2 = 38.1°C – 39.0°C; GRADE 3 = >39.0°C								



Supplementary Figure 1: Antibody responses to ChAdOx1 MERS by dose group.

Individual antibody responses for the three dose groups (A: Group 1, B: Group 2 and C: Group 3) at D0, D28, D56 time-points are shown. The correlation between the total IgG and neutralising antibody IC50 is shown for dose groups 1, 2, and 3 (D, E, and F, respectively).



Supplementary Figure 2: T cell responses to ChAdOx1 MERS for each vaccination group.

Total ex vivo IFN- γ ELISpot responses to MERS spike protein are shown for individual vaccinees from (A) Group 1, (B) Group 2 and (C) Group 3 at all timepoints.

King Abdullah International Medical Research Centre (KAIMRC)

And

UNIVERSITY OF OXFORD



A phase Ib study to determine the safety and immunogenicity of the candidate Middle East Respiratory Syndrome Coronavirus (MERS-CoV) vaccine ChAdOx1 MERS in healthy adult Middle Eastern volunteers

Study Code: MERS002

Protocol Number: CT18/004/R

Version: v1.2

Date: July 2019

Chief Investigator: Dr. Mohammad Bosaeed

Sponsor: KAIMRC

Funder: UK Department of Health (NIHR) through the University of Oxford

IRB Approval Number: IRBC/2079/18

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Full Study Title	A phase Ib study to determine the safety and immunogenicity of the candidate Middle East Respiratory Syndrome Coronavirus (MERS-CoV) vaccine ChAdOx1 MERS in healthy Middle Eastern adult volunteers Study Code: MERS002
Chief Investigator	Dr. Mohammad Bosaeed KAIMRC Email: bosaeedmo@NGHA.MED.SA
Trial Site	King Abdulaziz Medical City Ministry of National Guard Health Affairs, Riyadh, KSA.
Sponsoring Institution	King Abdullah International Medical Research Centre Ministry of National Guard Health Affairs, Riyadh, KSA
Monitor	KAIMRC Monitoring Unit
Data and Safety Management Board	To be identified by KAIMRC

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, members of the Research Ethics Committee and other regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Professor Hanan Balkhy.

Statement of Compliance

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP) Guideline, and all other applicable regulatory requirements.

Chief Investigator Approval and Agreement


I have read the trial protocol and agree to conduct the trial in compliance with the protocol, the principles of Good Clinical Practice and all applicable regulatory requirements.

I hereby approve this version of the protocol and declare no conflict of interest

Mohammad Bosaeed

Chief Investigator

Name



Signature

22/7/19

Date

Modification History

Version	Date	Author(s)	Co-Author(s)	Modifications
1.0		Naif Khalaf Alharbi and Hanan H. Balkhy	Pedro Folegatti, Sarah Gilbert, Adrian Hill	
1.1		Sultan Almaziad, Naif Khalaf Alharbi and Hanan H. Balkhy	Pedro Folegatti, Sarah Gilbert, Adrian Hill	
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1. SYNOPSIS

Trial Title	A phase Ib study to determine the safety and immunogenicity of the candidate Middle East Respiratory Syndrome Coronavirus (MERS-CoV) vaccine ChAdOx1 MERS in healthy adult Middle Eastern volunteers									
Trial Centre	King Abdulaziz Medical City Ministry of National Guard Health Affairs, Riyadh, KSA.									
Trial Identifier	MERS 002									
Clinical phase	Ib									
Study Design	Open–labelled, non-randomised, dose escalation, extension for a first-in-human, single centre, phase Ib clinical trial									
Population	Healthy Middle Eastern (who have the nationality of an Arab country) adults aged 18 – 50 years									
Planned Sample Size	24 volunteers <table><tr><th>Group</th><th>IMP</th></tr><tr><td>Group 1 (n=6)</td><td>5 x 10⁹ vp ChAdOx1 MERS</td></tr><tr><td>Group 2 (n=9)</td><td>2.5 x 10¹⁰ vp ChAdOx1 MERS</td></tr><tr><td>Group 3 (n=9)</td><td>5 x 10¹⁰ vp ChAdOx1 MERS</td></tr></table>		Group	IMP	Group 1 (n=6)	5 x 10 ⁹ vp ChAdOx1 MERS	Group 2 (n=9)	2.5 x 10 ¹⁰ vp ChAdOx1 MERS	Group 3 (n=9)	5 x 10 ¹⁰ vp ChAdOx1 MERS
Group	IMP									
Group 1 (n=6)	5 x 10 ⁹ vp ChAdOx1 MERS									
Group 2 (n=9)	2.5 x 10 ¹⁰ vp ChAdOx1 MERS									
Group 3 (n=9)	5 x 10 ¹⁰ vp ChAdOx1 MERS									
Follow-up duration	26 weeks post vaccine administration									
Planned Trial Period	Q2 2019 to Q2 2020									
Primary Objective	To assess the safety profile of the candidate vaccine ChAdOx1 MERS in healthy ME adult volunteers.									

Secondary Objective To assess the immunogenicity of the candidate vaccine ChAdOx1 MERS in healthy ME adult volunteers

Investigational Products ChAdOx1 MERS, a replication-deficient simian adenoviral vector expressing the spike (S) protein of MERS Coronavirus.

Dose per Administration ChAdOx1 MERS 5×10^9 vp
ChAdOx1 MERS 2.5×10^{10} vp
ChAdOx1 MERS 5×10^{10} vp

Form Liquid (all finished products)

Route Intramuscularly (IM) into the deltoid region of the arm

2. ABBREVIATIONS

AE	Adverse event
APP	Administrative Policies and Procedures
AR	Adverse reaction
CBF	Clinical Biomanufacturing Facility
ChAdOx1	Chimpanzee Adenovirus Ox1
ChAdOx1 MERS	Recombinant Chimpanzee Adenovirus Ox1 with MERS spike antigen
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trial Unit
DSMB	Data and Safety Management Board
DSUR	Development Safety Update Report
EC	Ethics committee
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunospot assay
FBC	Full blood count
GCP	Good Clinical Practice
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
HbA1c	Glycated Hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigators Brochure
ICH	International Conference on Harmonisation
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
KAIMRC	King Abdullah International Medical Research Centre
KAMC	King Abdulaziz Medical City
KASCH	King Abdullah Specialized Children Hospital
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency

MNGHA	Ministry of National Guard- Health Affairs
MVA	Modified Vaccinia Virus Ankara
pfu	plaque forming units
PIS	Participant information sheet
QP	Qualified Person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SFDA	Saudi Food & Drug Authority
SFU	Spot forming units
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
vp	Viral particles
WHO	World Health Organisation

3. BACKGROUND & RATIONALE

3.1 Impact of MERS-CoV and the need for a vaccine

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has been identified as one of the most worrying newly emerging outbreak pathogens by the World Health Organization (WHO), the National Institute of Allergy and Infectious Diseases (NIAID), the Center for Disease Control and Prevention (CDC), Public Health England (PHE) and many other global agencies and expert groups. The disease was first described in 2012 and is now endemic in Saudi Arabia. It has since spread to different countries in the Middle East and other regions, including a recent outbreak in South Korea. More than 2000 cases of severe acute respiratory disease; with more than 700 deaths in 27 countries have been reported (1).

The disease is caused by a Coronavirus and is spread by droplet and contact route from an infected human or from the camel, which is now known as the most likely animal host. Dromedary camels are now recognised as the source of zoonotic infections and occupational exposure may lead to symptomatic and asymptomatic disease in humans. Human to human transmission, specially in hospital environments, have been responsible for the majority of outbreaks and the majority have taken place in the Kingdom of Saudi Arabia. The clinical spectrum of MERS-CoV infection varies from asymptomatic or mild respiratory symptoms to severe acute respiratory illness and death. Common clinical symptoms include fever, cough and shortness of breath. Pneumonia is a common finding, but it might not always be present. Gastrointestinal symptoms, including diarrhoea, have also been reported. Severe illness can cause respiratory failure that requires mechanical ventilation and support in an intensive care unit. MERS-CoV has a reported case fatality rate of approximately 35%. The virus appears to cause more severe disease in the elderly, immunosuppressed and those with chronic diseases such as cardiovascular disease and diabetes (2-5).

The disease has been chosen as a very high priority disease for accelerated vaccine development by the WHO, international vaccine experts and by members of the UK Vaccines Research and Development network (6). Vaccines would be optimal to prevent disease in animals and humans. In addition the vaccination of workers who are occupationally exposed to camels would prevent them from becoming infected and limit the transmission of the virus to the wider population, in particular those at an increased risk of death such as the elderly or immunocompromised.

The dipeptidyl peptidase 4 (DPP4) receptor is used by the MERS-CoV virus during infection and is highly conserved between Camels and Humans. The MERS-CoV spike (S) protein is a characteristic structural component of the virion membrane and its S1 domain mediates binding to DPP4. The spike protein has been chosen as the target antigen for use in the replication-deficient simian adenovirus developed by the University of Oxford, ChAdOx1 vaccine vector. ChAdOx1 has shown successful results in the development of Oxford lead vaccines which have gone on to enter phase I trials within the UK (7). In this study we propose the clinical testing of the ChAdOX1 MERS vaccine, which is manufactured to GMP

by the CBF, Oxford, UK; in Middle Eastern adults, following a first-in-human phase I trial conducted in Oxford.

3.2 Progress towards a MERS vaccine

Global efforts to develop a coronavirus vaccine faded in the aftermath of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) pandemic but has since gained renewed momentum in the face of the current MERS-CoV outbreak. Most of the developed vaccines were based on the S surface glycoprotein, the primary target for neutralizing antibodies during any natural coronavirus infection. A number of preclinical and clinical studies showed that the SARS-CoV S1 protein subunit, and specifically the Receptor Binding Domain (RBD) at its core, could serve as a dominant target for neutralizing antibodies in mice, non-human primates, and humans. S1, therefore, became the basis for a number of promising SARS-CoV vaccine candidates (8).

The S1 protein subunit and the RBD have also been the basis for several MERS-CoV vaccine candidates. Both constructs have elicited neutralizing antibodies of high potency across multiple viral strains. Despite their demonstrated immunogenicity in animal models and anticipated safety in humans, RBD or S1-subunit based vaccine candidates are limited in their epitope breadth. Vaccine candidates that elicit a more diverse antibody repertoire as well as a robust cellular immune response may offer the advantage of broader and more durable protection (8).

Live attenuated viruses have historically been among the most immunogenic platforms available, as they have the capacity to present multiple antigens across the viral life cycle in their native conformations. However, manufacturing live-attenuated viruses requires complex containment and biosafety measures. Furthermore, live-attenuated viruses carry the risks of inadequate attenuation causing disseminated disease, particularly in immunocompromised hosts. Given that moderately immuno-compromised adults with co-morbidities have suffered the most severe MERS-CoV disease, making a live-attenuated virus vaccine is a less viable option. Replication competent viral vectors could pose a similar threat for disseminated disease in the immuno-suppressed. Replication deficient vectors, however, avoid that risk while maintaining the advantages of native antigen presentation, elicitation of T cell immunity and the ability to express multiple antigens (8).

Several recombinant DNA, protein and viral vectored MERS-CoV candidate vaccines have been developed and tested in animal models (mice, non-human primates and camels) with varied efficacy results. Recently, a recombinant MVA encoding the full length Spike protein antigen (S) showed partial efficacy by significantly reducing MERS-CoV viral shedding in a camel challenge study. (9, 10)

The first MERS-CoV vaccine to be used in humans has recently entered a phase I dose ranging safety study in January 2016. The GLS-5300, a DNA plasmid vaccine that expresses the MERS-CoV spike (S) glycoprotein, is being administered to 75 healthy adult volunteers in

the USA, by the Walter Reed Army Institute of Research. Safety and immunogenicity data are expected to be reported by the end of 2018.

3.3 MERS-CoV spike protein as a vaccine antigen

Coronaviruses (CoVs) are spherical and enveloped viruses with large, unsegmented, single positive RNA genomes. One-third of the genome is responsible for coding the structural proteins: spike (S) glycoprotein, small envelope protein (E), integral membrane protein (M), and genome-associated nucleocapsid protein (N). The proteins E, M, and N are mainly responsible for the assembly of the virions, while the S protein is involved in receptor binding and bears membrane fusion capabilities during CoVs infection. Thus, the S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range (11).

S is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spikeshaped protrusions from the virion. S is 1353 amino acids in length, heavily glycosylated (with 21 predicted N-linked glycosylation sites), and consists of a large ectodomain and a short cytosolic tail. The S proteins of CoVs can be divided into two functional subunits: the N-terminal S1 subunit forms the globular head, and the membrane-embedded C-terminal S2 (11). S1 and S2 subunits are respectively, responsible for cellular receptor DPP4 binding via the RBD, and fusion of virus and cell membranes, thereby mediating the entry of MERS-CoV into the target cells. The MERS-CoV RBD consists of a core structure, which is homologous to that of the SARS-CoV S protein RBD, and a receptor-binding motif, which is unique to MERS-CoV, thus determining viral pathogenesis and receptor recognition (12).

The roles of S in receptor binding and membrane fusion make it a perfect target for vaccine and antiviral development. Previous studies on SARS-CoV reveal that vaccines based on the S protein can induce antibodies to block virus binding and fusion or neutralize virus infection (11). ChAdOx1 MERS expresses a codon-optimised coding sequence for the Spike protein from the MERS-CoV isolate Camel/Qatar_2_2014 (GenBank:KJ650098.1).

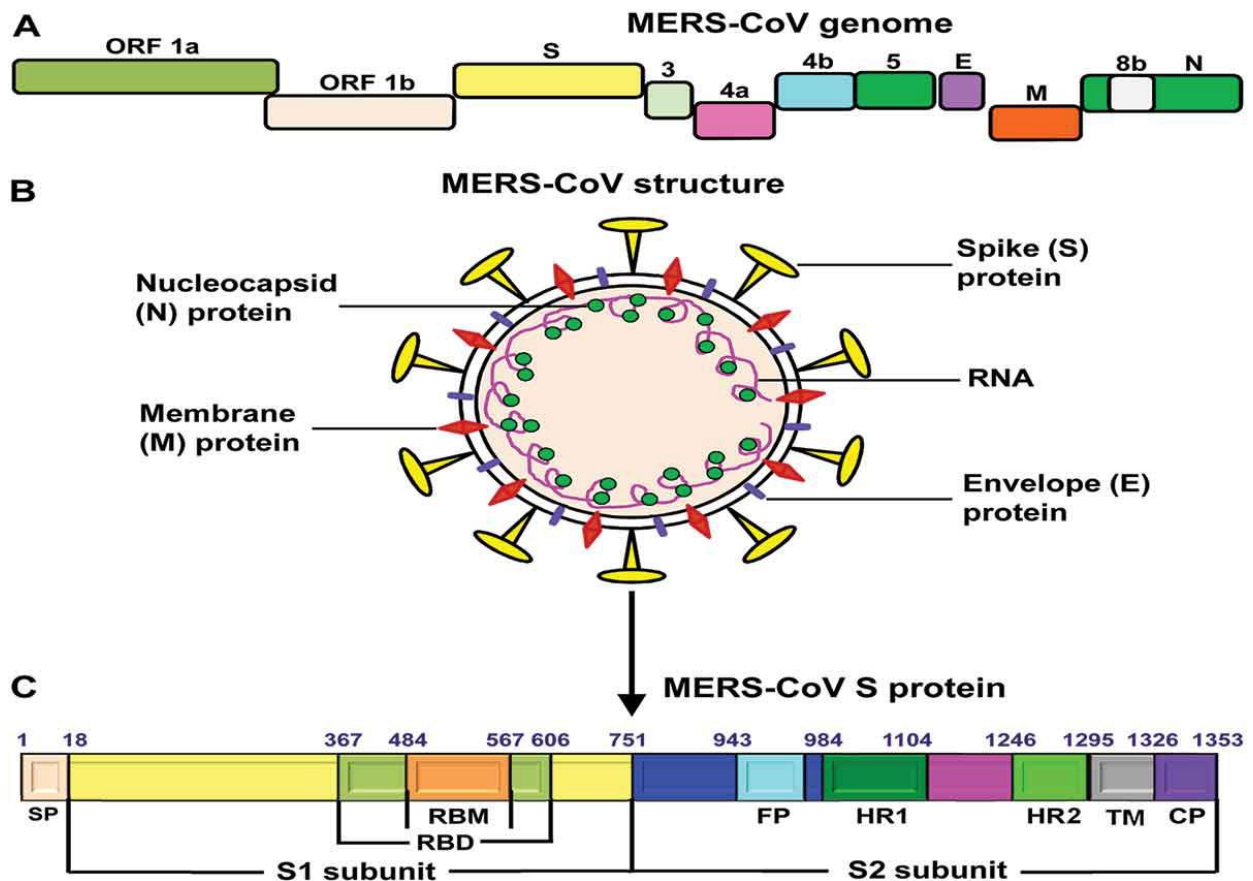


Figure 1. MERS-CoV structure. Published in: Lanying Du; Wanbo Tai; Yusen Zhou; Shibo Jiang; Expert Review of Vaccines (12)

3.4 Adenovirus-vectored Vaccines

Adenoviruses are attractive vectors for human vaccination. They possess a stable genome so that inserts of foreign genes are not deleted and they can infect large numbers of cells without any evidence of insertional mutagenesis.

Replication defective adenovirus can be engineered by deletion of genes from the E1 locus, which is required for viral replication, and these viruses can be propagated easily with good yields in cell lines expressing E1 from AdHu5 such as human embryonic kidney cells 293 (HEK 293 cells) (13).

Previous mass vaccination campaigns in over 2 million adult US military personnel using orally administered live human adenovirus serotype 4 and 7 have shown good safety and efficacy data (14). Human adenoviruses are under development as vectors for malaria, HIV and hepatitis C vaccines, amongst others. They have been used extensively in human trials with excellent safety profile mainly as vectors for HIV vaccines.

A limiting factor to widespread use of human adenovirus as vaccine vectors has been the level of anti-vector immunity present in humans where adenovirus is a ubiquitous infection. The prevalence of immunity to human adenoviruses prompted the consideration of simian adenoviruses as vectors, as they exhibit hexon structures homologous to human

adenoviruses (15). Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US.

In chimpanzee adenoviruses, the E1 locus can be deleted to render viruses replication deficient and allow transcomplementation on an E1 AdHu5 complementing cell line (16). Whilst they exhibit hexon structures homologous to that of human adenoviruses (17), the lack of sequence homology at the E1 flanking sequence prevents homologous recombination and production of replication competent virus (18)

Chimpanzee adenoviral vectors can be manufactured cost-effectively and are now in clinical development as possible vaccines against malaria, HIV, tuberculosis, influenza, hepatitis C, RSV, Cancer and Ebola.

3.5 ChAdOx1

ChAdOx1 is a novel recombinant chimpanzee adenovirus designed as a vaccine vector, developed by The Jenner Institute at the University of Oxford. This viral vector has been used by researchers at the University of Oxford to produce a number of vaccines expressing a range of different antigens. Three phase I clinical trials have been completed in the UK using ChAdOx1 with different inserts (two influenza trials and one TB trial).

ChAdOx1 is produced from a replication-deficient (E1 and E3 deleted) simian adenovirus and it has been described by Dicks et al (19). The vector was constructed in a bacterial artificial chromosome (BAC) to facilitate genetic manipulation of genomic clones with improved stability and flexibility. Cellular immunogenicity of recombinant E1 E3-deleted ChAdOx1 was comparable to that of other species E derived chimpanzee adenovirus vectors including ChAd63, the first simian adenovirus vector to enter clinical trials in humans. The E1 region is essential for viral replication, hence the ability to delete E1 renders the new vector immediately replication incompetent. The deletion of the non-essential adenovirus E3 region increases the insert capacity of the new vector by approximately 5kb. It is known that the proteins encoded by the E4 region of adenoviruses interact with E1 during viral replication, and the imperfect interaction between the gene products of the AdHu5 E1 gene produced by HEK293 cells and simian E4 gene products has been found to result in impaired viral replication in this cell line, and consequently lower virus yields. In ChAdOx1, Ad5 E4Orf4 has been inserted to replace the homologous simian virus coding sequence, resulting in improved viral replication during vaccine production. Since no replication of the virus takes place after immunization, this replacement has no effect on immunogenicity of the viral vector. Insertion of recombinant antigens at the E1 locus is performed using Gateway® site specific recombination technology (Invitrogen).

3.6 Development of ChAdOx1 MERS

ChAdOx1 MERS encodes the Spike (S) surface glycoprotein of the coronavirus. A genomic clone of ChAdOx1 MERS was prepared by Gateway® recombination between an entry plasmid containing the codon-optimised coding sequence for Spike protein from the MERS-CoV isolate Camel/Qatar_2_2014 (GenBank:KJ650098.1), and the E1-and E3-deleted ChAdOx1 destination vector.

3.7 Preclinical Studies

3.7.1 Efficacy and Immunogenicity

Mice (balb/c) were immunised with ChAdOx1 or MVA vectored vaccines expressing MERS-CoV Spike protein. Serum samples were taken after 28 days and endpoint titres measured by ELISA. This study showed that a single dose of ChAdOx1 results in equivalent immunogenicity to two doses of MVA (20).

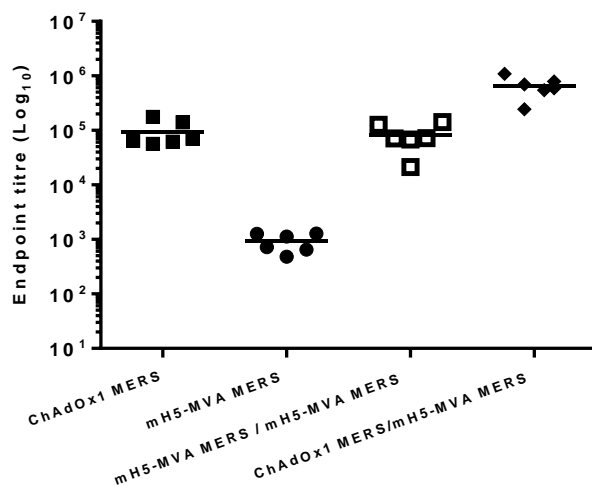


Figure 2. Immunogenicity of viral vectored vaccines MERS vaccines in mice, Alharbi, N.K. *et al* (20).

An efficacy preclinical study has been conducted where mice transgenic for the hDPP4 receptor were immunised with a single dose of ChAdOx1 MERS by either intranasal or intramuscular injection. The control ChAdOx1 vaccine expressed eGFP as the vaccine antigen. Serum neutralising titres were measured 28 days after vaccination, when the mice were then challenged with MERS CoV by intranasal inoculation. The results showed that mice immunised with the MERS vaccine by either route were completely protected against MERS-CoV infection. No virus was detected in the lungs of the mice receiving the MERS vaccine and they all survived, whereas all of the sham-vaccinated mice succumbed to infection within 8 days (Vincent Munster, unpublished data).

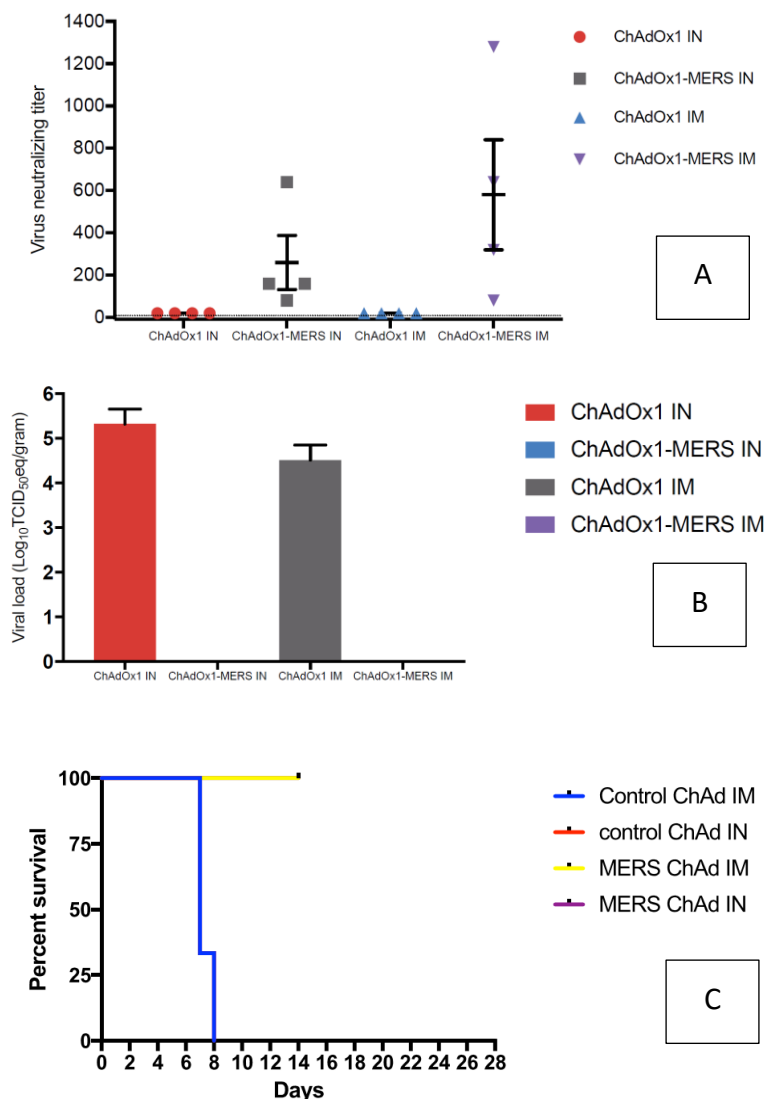


Figure 3. **A.** Virus neutralising titres in mice amongst ChAdOx1 MERS and controls administered via intranasal or intramuscularly. **B.** Viral load after MERS-CoV challenge. **C.** Survival amongst ChAdOx1 MERS and control mice after intranasal MERS-CoV challenge Munster, V. *et al* (21).

3.8 Previous clinical experience

This will be the second study employing ChAdOx1 MERS in humans. However, ChAdOx1 vectored vaccines expressing different inserts have previously been used in 161 (as of DEC 2017) healthy volunteers taking part in clinical trials conducted by the University of Oxford in the UK (table 1).

ChAdOx1 encoding the influenza fusion protein NP+M1 has been safely administered to 84 healthy adult volunteers in the UK in two completed clinical trials conducted at The Jenner Institute (FLU004 and FLU005). FLU004 was a phase I, open-label, non-randomised dose escalation study of ChAdOx1 NP+M1. The vaccine was safe, well tolerated and

immunogenic, inducing ELISpot responses at all doses. The dose of 2.5×10^{10} vp was chosen for further studies of ChAdOx1 NP+M1 (7).

FLU005 was a multicentre phase I, randomised study to determine the safety and immunogenicity of vaccination regimens employing the candidate influenza vaccines MVA-NP+M1 and ChAdOx1 NP+M1. Sixty-nine healthy adult volunteers have received ChAdOx1 NP+M1 at a dose of 2.5×10^{10} vp. Administrations of ChAdOx1 NP+M1 and MVA-NP+M1 vaccines were found to be safe and well-tolerated, in agreement with our previous studies (7, 22-24). The majority of adverse events were mild to moderate in nature and lasted for 1-2 days. The most common local adverse event was arm pain at the site of injection and the most common systemic adverse event was mild fatigue and headache.

TB034 was an open-label, phase I clinical trial in which 42 healthy adult volunteers received the ChAdOx1 viral vector expressing the *Mycobacterium tuberculosis* antigen 85A (ChAdOx1 85A). No major safety concerns associated with ChAdOx1 85A administration have been reported.

ChAdOx1 5T4 has been given in the VANCE01 study which is an ongoing first-in-man open label randomized phase I study to determine the safety and immunogenicity of heterologous prime boost ChAd-MVA vaccination against oncofetal antigen 5T4. To date, 34 participants have received the ChAdOx1 5T4 vaccine at a dose of 2.5×10^{10} vp and only mild AEs related to the vaccination have been reported

VAC067 was a first human study of the ChAdOx1 viral vector expressing dual second generation liver-stage malaria antigens LSA1 and LSAP2 (ChAdOx1 LS2). No significant safety concerns have been reported.

None of the above mentioned clinical trials reported serious adverse events associated with the administration of ChAdOx1, which was shown to have a good safety profile.

Table 1. Clinical experience with ChAdOx1 viral vector vaccines.

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)
UK	FLU004	ChAdOx1 NP+M1	18-50	IM	5×10^8 vp	3
					5×10^9 vp	3
					2.5×10^{10} vp	3
					5×10^{10} vp	6
UK	FLU005	ChAdOx1 NP+M1 MVA NP+M1 (week 8)	18-50	IM	2.5×10^{10} vp	12
		ChAdOx1 NP+M1 MVA NP+M1 (week 52)	18-50	IM	2.5×10^{10} vp	12

		MVA NP+M1 ChAdOx1 NP+M1 (week 8)	18-50	IM	2.5×10^{10} vp	12
		MVA NP+M1 ChAdOx1 NP+M1 (week 52)	18-50	IM	2.5×10^{10} vp	9
		ChAdOx1 NP+M1	>50	IM	2.5×10^{10} vp	12
		ChAdOx1 NP+M1 MVA NP+M1 (week 8)	>50	IM	2.5×10^{10} vp	12
UK	TB034	ChAdOx1 85A	18-50	IM	5×10^9 vp	6
		ChAdOx1 85A	18-50	IM	2.5×10^{10} vp	12
		ChAdOx1 85A MVA85A (week 8)	18-50	IM	2.5×10^{10} vp	12
UK	VANCE01 (ongoing)	ChAdOx1.5T4 MVA.5T4	18 – 75	IM	2.5×10^{10} vp	34 (*as of Dec 2017)
UK	VAC067	ChAdOx1 LS2	18-45	IM	5×10^9 vp	3
		ChAdOx1 LS2	18-45		2.5×10^{10} vp	10
UK	MERS001	ChAdOx1 MERS (ongoing)	18-50	IM	5×10^9 vp	Update available upon request
					2.5×10^{10} vp	Update available upon request
					5×10^{10} vp	Update available upon request

3.9 Rationale

MERS-CoV is an emerging zoonotic viral disease considered a global threat and listed as a priority pathogen for urgent Research and Development. The recent MERS-CoV outbreaks in the Middle East (from 2012 and still ongoing) and South Korea (2015) have caused a total of 782 deaths representing a case fatality rate of approximately 35% and imported cases have now been reported in 27 countries (1).

Chimpanzee adenovirus vaccine vectors have been safely administered to thousands of people using a wide range of infectious disease targets including malaria (25), HIV (26), tuberculosis, influenza (7), hepatitis C (27), RSV (28) and most recently Ebola (29). ChAdOx1 viral vectored vaccines have shown to be both safe and immunogenic in previous clinical trials in the UK (FLU004, FLU005, TB034, VANCE001 and VAC067). Single-dose immunisation with ChAdOx1 MERS vaccine has shown to elicit high levels of neutralising antibody in animal models.

Finally, the One Health vaccine development approach used here, by which the same vaccine is co-developed for humans and susceptible animal species, is well suited to many emerging outbreak pathogens, most of which involve zoonotic transmission (30). The approach allows the possibility of cost reductions for the final product by increasing the scale of manufacture (31). Ultimately the vaccine could be licensed for use in camels in the Middle East and North Africa. If licensed, human vaccines could be deployed for occupationally exposed individuals such as camel workers and health care professionals, with stockpiles available for use in the case of an outbreak.

3.10 Vaccine Development Strategy

The data from this study will be used to support a phase II study in the Middle East and Africa.

4. OBJECTIVES AND ENDPOINTS

The number of volunteers has been chosen to generate adequate safety and immunogenicity data to meet these objectives, whilst minimising the number of volunteers exposed to a new vaccination regimen.

4.1 Primary Objective

To assess the safety and tolerability of ChAdOx1 MERS in healthy ME adult volunteers.

4.1.1 Primary Outcome Measures

The specific endpoints for safety and reactogenicity will be actively and passively collected data on adverse events.

The following parameters will be assessed for all study groups

- Occurrence of solicited local reactogenicity signs and symptoms for 7 days following the vaccination
- Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following the vaccination
- Occurrence of unsolicited adverse events for 28 days following the vaccination
- Change from baseline for safety laboratory measures
- Occurrence of serious adverse events during the whole study duration

Volunteers will undergo clinical follow up for adverse events for a further 182 days (6.5 months) following completion of the vaccination regimen. SAEs will be collected throughout the study. The duration of follow up reflects the desire to obtain longer term safety data with the first use of ChAdOx1 MERS in humans.

4.2 Secondary Objective

To assess the cellular and humoral immunogenicity of ChAdOx1 MERS in healthy ME adult volunteers.

4.2.1 Secondary Outcome Measures

Measures of immunogenicity to the ChAdOx1 MERS vaccine may include:

- ELISA to quantify antibodies to MERS Spike protein antigen
- Ex vivo ELISpot responses to MERS Spike protein antigen

Other exploratory immunology may be carried out in collaboration with other specialist laboratories, including laboratories outside of Saudi Arabia. This would involve transfer of serum/plasma and/or peripheral blood mononuclear cells (PBMC), but samples would be anonymised. Volunteers will be consented for this.

5. STUDY OVERVIEW

This is an open-label, dose escalation phase 1b trial to assess the safety and immunogenicity of the candidate ChAdOx1 MERS vaccine in healthy Middle Eastern adult volunteers aged 18-50. The first-in-human trial is now being conducted in Oxford in UK healthy adult volunteers. The vaccine will be administered intramuscularly.

Volunteers will be recruited and vaccinated at the King Abdulaziz Medical City, M-NGHA, Riyadh. There will be 3 study groups and a total of 24 volunteers will be enrolled (table 2). Staggered enrolment will apply for the first three volunteers within each group. Volunteers will be first recruited into Group 1 and subsequently into Groups 2 and 3 following interim clinical safety reviews (see section 7.4.2). Volunteers will be allocated to a study group by selecting eligible volunteers for enrolment in the order in which they were deemed eligible, following screening.

5.1 Rationale for Selected Doses

Doses to be administered in this trial have been selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts and similar adenovirus vectored vaccines (eg. ChAd63).

A first-in-man dose escalation study using the ChAdOx1 vector encoding an influenza antigen (FLU004), safely administered ChAdOx1 NP+M1 at doses ranging from 5×10^8 to 5×10^{10} vp. Subsequent review of the data identified an optimal dose of 2.5×10^{10} vp balancing immunogenicity and reactogenicity. This dose has subsequently been given to over 100 volunteers in numerous larger phase 1 studies at the Jenner Institute (FLU005, TB034 VANCE01 and VAC067) and ChAdOx1 vectored vaccines have thus far demonstrated to be very well tolerated. The vast majority of AEs have been mild-moderate and there have been no SARs until this date.

Another simian adenovirus vector (ChAd63) has been safely administered at doses up to 2×10^{11} vp with an optimal dose of 5×10^{10} vp, balancing immunogenicity and reactogenicity.

The first dose of ChAdOx1 MERS proposed in the first-in-human assessment of the MERS-CoV S antigenic insert conducted in Oxford was 5×10^9 vp. Doses will be gradually increased aiming to provide an optimal dose of ChAdOx1 MERS considering the tolerability, reactogenicity and immunogenicity profiles up to 5×10^{10} vp.

5.2 Study Groups

Table 2. Study Groups

Group	IMP
Group 1 (n=6)	5×10^9 vp ChAdOx1 MERS
Group 2 (n=9)	2.5×10^{10} vp ChAdOx1 MERS

Group 3 (n=9)	5 x 10 ¹⁰ vp ChAdOx1 MERS
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5.2.1 First Volunteers

Volunteers will be enrolled and doses will be escalated according to the plan outlined below.

The first volunteer in the study will receive 5 x 10⁹vp of ChAdOx1 MERS (group 1). This volunteer will be vaccinated ahead of any other volunteer and the profile of adverse events will be examined after 48h. Provided there are no safety concerns as assessed by the Chief Investigator (CI) and Data and Safety Management Board (DSMB), another 2 volunteers will be vaccinated at the same dose after at least 48 hours has elapsed following vaccination of the first volunteer and at least 1 hour apart from each other. An independent safety review will be conducted by the DSMB after vaccination of the first 3 volunteers in group 1. This review will include the results of safety blood tests at day 7 post vaccination and an assessment of the profile of the adverse events reported. The CI and the DSMB will be asked to provide the decision on whether to proceed with vaccinations of the remaining participants in group 1 and the first volunteer to receive the next incremental dose in group 2, and a decision on whether to monitor the remaining volunteers in group 1 in CTU. If there are no safety concerns, the remaining volunteers in Group 1 and the first volunteer in group 2 may be vaccinated.

The same procedure will apply for each of the first 3 volunteers enrolled at higher dosage group prior to dose escalation (groups 2 and 3).

5.2.2 Duration of study

The total duration of the study will be 26 weeks from the day of enrolment for all volunteers.

5.2.3 Definition of Start and End of Trial

The start of the trial is defined as the date of the first vaccination of the first volunteer. The end of the trial is the date of the last visit of the last volunteer.

5.3 Potential Risks for volunteers

The potential risk to participants is considered as low. The potential risks are those associated with phlebotomy and vaccination. In general, recombinant adenoviral vectors are safe. Similar vaccines encoding different antigens have been given to several thousand volunteers (including children) with a good safety profile.

Phlebotomy:

The maximum volume of blood drawn over the study period (approximately 285mL) should not compromise these otherwise healthy volunteers. There may be minor bruising, local tenderness or pre-syncope symptoms associated with venepuncture, which will not be documented as AEs if they occur.

Vaccination:

ChAdOx1 MERS has not been used in humans in KSA (or in ME volunteers) before and therefore will be initially administered at the lower dose of 5×10^9 vp before progressing to the higher dose 2.5×10^{10} vp and 5×10^{10} vp in Groups 2 and 3. Potential expected risks from vaccination include local effects such as pain, redness, warmth, swelling, tenderness or itching. Systemic reactions that could potentially occur following immunisation with a recombinant adenovirus vaccine include a flu-like illness with feverishness, fatigue, malaise, arthralgia, myalgia and headache.

As with any vaccine, Guillain-Barré syndrome or immune-mediated reactions that can lead to organ damage may occur, but this should be extremely rare. Serious allergic reactions including anaphylaxis could also occur and for this reason volunteers will be vaccinated in a clinical area where Advanced Life Support trained physicians, equipment and drugs are immediately available for the management of any serious adverse reactions (SAR).

5.4 Known Potential Benefits

Volunteers will not benefit directly from participation in this study. However, it is hoped that the information gained from this study will contribute to the development of a safe and effective MERS-CoV vaccine regime. The only benefits for participants would be information about their general health status.

Health care access and eligibility for treatment at Ministry of National Guard health care facilities shall be granted to all volunteers (see section 15.2). The main reason is to ensure the safety and well-being of volunteers during and after the study is completed. Due to the nature of health care access in Saudi Arabia, It can be potentially considered as indirect benefits for enrolling in the study .

6. RECRUITMENT AND WITHDRAWAL OF TRIAL VOLUNTEERS

6.1 Volunteers

Volunteers will be recruited by use of an advertisement +/- registration form formally approved by the ethics committee (and the M-NGHA IRB) and distributed or posted in the following places:

- In public places, including buses and trains, with the agreement of the owner/proprietor.
- In newspapers or other literature for circulation.
- On radio via announcements.
- On a website or social media site operated by our group or with the agreement of the owner or operator (including on-line recruitment through our web-site).
- By e-mail distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation.
- By email distribution to individuals who have already expressed an interest in taking part in any clinical trial of KAIMRC.
- On stalls or stands at exhibitions or fairs.
- Via presentations (e.g. presentations at lectures or invited seminars).

6.2 Informed consent

All volunteers will sign and date the informed consent form before any study specific procedures are performed. The information sheet will be made available to the volunteer at least 24 hours prior to the screening visit. At the screening visit, the volunteer will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The volunteer may withdraw from the study at any time
- The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational vaccine
- There is no personal benefit from participating
- The volunteer may be assigned to a primary care physician and/or specialist during screening or subsequent visits, if necessary.
- The primary doctor of volunteer will be contacted to corroborate their medical history.
-
- The volunteer's blood samples taken as part of the study will be stored indefinitely and samples may be sent outside of Saudi Arabia to laboratories in collaboration

with KAIMRC such as the University of Oxford, thus, These samples will be anonymised.

The aims of the study and all tests to be carried out will be explained. The volunteer will be given the opportunity to ask about details of the trial and will then have time to consider whether or not to participate. If they do decide to participate, they will sign and date two copies of the consent form, one for them to take away and keep, and one to be stored in the case report form (CRF) – this is a paper or electronic document used to collect data relating to a particular volunteer. These forms will also be signed and dated by the Investigator.

6.3 Inclusion and exclusion criteria

This study will be conducted in healthy ME adult volunteers, who meet the following inclusion and exclusion criteria:

6.3.1 Inclusion Criteria

The volunteer must satisfy all the following criteria to be eligible for the study:

1. Healthy* ME adults aged 18 to 50 years
2. Able and willing (in the Investigator's opinion) to comply with all study requirements
3. Willing to allow the investigators to access the volunteer's medical history.
4. For females only, not planning to get pregnant during the study and a negative pregnancy test on the day(s) of screening and vaccination. Effective methods of contraception must be used. See section 6.3.3
5. Agreement to refrain from blood donation during the course of the study
6. Provide written informed consent

* The Royal College of Physicians has defined the healthy volunteer as an "individual who is not known to suffer of any significant illness relevant to the proposed study, who should be within the ordinary range of body measurements, such as weight, and whose mental state is such that he is able to understand and give valid consent to the study". In this study, healthy adults refer to those who don't suffer from chronic diseases and fitting the above mentioned definition.

6.3.2 Exclusion Criteria

The volunteer may not enter the study if any of the following apply:

1. Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period
2. Prior receipt of an investigational vaccine likely to impact on interpretation of the trial data.

3. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate
4. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent, severe infections and chronic (more than 14 days) immunosuppressant medication within the past 6 months (inhaled and topical steroids are allowed)
5. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine
6. Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
7. Any history of anaphylaxis in relation to vaccination
8. Pregnancy, lactation or willingness/intention to become pregnant during the study
9. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
10. History of serious psychiatric condition likely to affect participation in the study
11. Bleeding disorder (eg. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
12. Any other serious chronic illness requiring hospital specialist supervision
13. Suspected or known current alcohol use.
14. Suspected or known drug abuse in the 5 years preceding enrolment
15. Seropositive for hepatitis B surface antigen (HBsAg)
16. Seropositive for hepatitis C virus (antibodies to HCV)
17. Any clinically significant abnormal finding on screening biochemistry or haematology blood tests or urinalysis
18. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data
19. History of exposure to MERS-CoV *
20. History of contact with camels. Defined as working in farms or barns; having been within 6 feet (2 meters) of a sick camel without PPE; or consumption of raw milk or uncooked meat. For this study, 30 days prior to screening will be considered.
21. History of allergic reaction to Aminoglycoside antibiotics.

*rRT-PCR testing of nasopharyngeal specimen , at the discretion of PI, may be indicated when a volunteer is suspected to be asymptomatic carrier.

6.3.3 Effective contraception for female volunteers

Female volunteers are required to avoid pregnancy during the course of the study (i.e until their last follow up visit). As this is a Phase Ib, study there is no information about the effect of this vaccine on a foetus. Male subjects with female partners of child-bearing potential are

not required to use barrier contraception whilst taking part in this study as the risk of excretion of the vaccine is negligible.

Acceptable forms of contraception for female volunteers include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception (condom or occlusive cap with spermicide)
- True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception

6.3.4 Prevention of 'Over Volunteering'

Volunteers will be excluded from the study if they are concurrently involved in another trial. In order to check this, volunteers will be asked to provide their National ID number or Passport number and details will be recorded in registration/screening forms.

6.3.5 Criteria for postponement of vaccination

The following events constitute contraindications to administration of the vaccine at that point in time; if any one of these events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, or withdrawn at the discretion of the Investigator.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. Although all vaccines can be administered safely to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile fever, postponement of vaccination will be considered.
- Temperature of $>37.5^{\circ}\text{C}$ (99.5°F) at the time of vaccination, measured orally.

6.3.6 Withdrawal of Volunteers

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a volunteer has the right to withdraw from the study at any time and for any reason and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the volunteer at any time in the interests of the volunteer's health and well-being. In addition, the volunteer may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator.
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation.

- Volunteer non-compliance with study requirements.
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. Any volunteer who is withdrawn from the study may be replaced, if that is possible within the specified time frame. The DSMB may recommend withdrawal of volunteers.

Any volunteer who fails to attend for two or more follow-up visits during the study will be deemed to have withdrawn from the study.

If a volunteer withdraws from the study, blood samples collected before their withdrawal from the trial will be used/ stored unless the volunteer specifically requests otherwise.

In all cases of subject withdrawal, excepting those of complete consent withdrawal, long-term safety data collection, including some procedures such as safety bloods, will continue as appropriate if subjects have received one or more vaccine doses.

6.4 Compliance with Dosing Regime

Each volunteer will receive a single dose of the vaccine administered once by the investigator and compliance will, therefore, not be an issue.

6.5 Pregnancy

Only females not planning to get pregnant will be enrolled in the study. Volunteers will consent for, and will be having pregnancy tests during screening and vaccination visits. Should a volunteer become pregnant during the trial (after having the vaccine), she will be followed up as other volunteers and her results will be included in the analysis; in addition, she will be followed until pregnancy outcome. Shall a volunteer become pregnant before the vaccination, she will be excluded from the trial.

7. CLINICAL PROCEDURES

This section describes the clinical procedures for evaluating study participants and follow-up after administration of study vaccine.

7.1 Study procedures

All volunteers will have the same schedule of clinic attendances and procedures as indicated in the schedules of attendance (Table 4). All subjects will receive the ChAdOx1 MERS vaccine, and undergo follow-up for a total of 26 weeks. The total volume of blood donated during the study will be approximately 285mL. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, urine microscopy in the event of positive urinalysis or additional blood tests if clinically relevant (see 7.3).

7.2 Observations

Pulse, blood pressure and temperature will be measured at the time-points indicated in the schedule of procedures and may also be measured, in addition to non-invasive tests (ECG), as part of a physical examination if indicated at other time-points.

7.3 Blood Tests and Urinalysis

Blood will be drawn for the following laboratory tests and processed:

1. At King Abdulaziz Medical City, National Guard Health Affairs, Riyadh using standard procedures:
 - **Haematology;** Full Blood Count
 - **Biochemistry;** Sodium, Potassium, Urea, Creatinine, Albumin, Liver Function Tests (ALT, ALP, Bilirubin), β -HCG for female participants at screening and prior to each vaccine dose
 - **Diagnostic serology;** HBsAg, HCV antibodies, HIV antibodies (specific consent will be gained prior to testing blood for these blood-borne viruses)
 - **Immunology;** Human Leukocyte Antigen (HLA) typing

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigators. These generally include, but are not limited to Hb A1c, AST, GGT and a coagulation screen.

2. At KAIMRC Infectious Diseases Research laboratories:

- **Exploratory Immunology;** Immunogenicity will be assessed by a variety of immunological assays. This may include antibodies to MERS-CoV Spike protein, ex

vivo ELISpot assays for interferon gamma and flow cytometry assays. Other exploratory immunological assays including cytokine analysis and other antibody assays, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed at the discretion of the Investigators.

3. **Urinalysis;** Urine will be tested for protein, blood and glucose at screening. This will be tested at King Abdulaziz Medical City, National Guard Health Affairs, Riyadh.
4. **Drug testing:** As per SOP 9812/AR/D06VOI/S02VOI, Testing Subjects for Drug Abuse in Phase 1 Clinical Trials.

Collaboration with other specialist laboratories in the UK and Europe for further research exploratory immunological tests may occur. This would involve the transfer of serum or plasma and/or PBMC to these laboratories, but these would remain anonymised. This will be included in the Informed consent from volunteers. Immunological assays will be conducted according to local SOPs at these international laboratories.

Subjects will be informed that there may be leftover samples of their blood (after all testing for this study is completed), and that such samples may be stored in the Saudi National Biobank at KAIMRC for possible future research (exploratory immunology), including human DNA and RNA analyses to search for correlates of vaccine immunogenicity and efficacy. Subjects will be able to decide if they will permit such future use of any leftover samples. With the volunteers' informed consent, any leftover cells, urine and serum/plasma will be frozen indefinitely for future ethically approved research studies of MERS-CoV specific or vaccine-related responses. If a subject elects not to permit this, all of that subject's leftover samples will be discarded after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

7.4 Study visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances (Table 4). Each visit is assigned a time-point and a window period, within which the visit will be conducted. On the day of each visit, the subject will be called by the assigned study coordinator and when arrives at the at the KASCH parking entrance, the subject will be escorted by the coordinator through the designated elevator straight to the phase 1 unit reception in the 8th floor at KASCH building.

7.4.1 Screening visit

All potential volunteers will have a screening visit, which may take place up to 90 days prior to vaccination. Informed consent will be taken before screening, as described in section 6.2. If consent is obtained, the screening procedures indicated in the schedule of attendances will be undertaken.

The subject's medical history will be accessed by the PI with the written permission (included in the consent form) after satisfactory screening to ascertain any significant medical history.

Abnormal clinical findings from the urinalysis or blood tests at screening will be assessed by the lead clinician according to section 9 below. Abnormal blood tests following screening will be assessed according to site-specific laboratory adverse event grading tables adapted from FDA, which are filed in the trial master file (TMF) or the Investigator Site File (ISF). Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, additional testing may be ordered and the volunteer will be informed and appropriate medical care arranged with the permission of the volunteer.

The eligibility of the volunteer will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator. If eligible, a day 0 visit will be scheduled for the volunteer to receive the vaccine.

7.4.2 Day 0: Enrolment and Vaccination Visit

Volunteers will not be considered enrolled in the study until they have received a vaccine. Before vaccination, the eligibility of the volunteer will be reviewed. Pulse, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine need to postpone vaccination depending on criteria listed in section 6.3.5. Vaccinations will be administered as described below.

7.4.2.1 Vaccinations

Before each vaccination, the on-going eligibility of the volunteer will be reviewed. All vaccines will be administered intramuscularly as described below in section 8.4. The injection site will be covered with a sterile dressing and the volunteer will stay in the trial site for observation for 48 hours, and closely observed in the first hour in case of immediate adverse events. Observations will be taken 30 minutes after vaccination (+/- 5 minutes) and the sterile dressing removed and injection site inspected. Observations will also be taken again at 60 minutes (+/- 10 minutes) and, in case of in-unit observation, every 12 hours thereafter until immediately before the volunteers leave the trial site. An oral thermometer, tape measure and diary card (paper or electronic) will be given to each volunteer, with

instructions on use, along with the emergency 24 hour telephone number to contact the on-call study physician if needed.

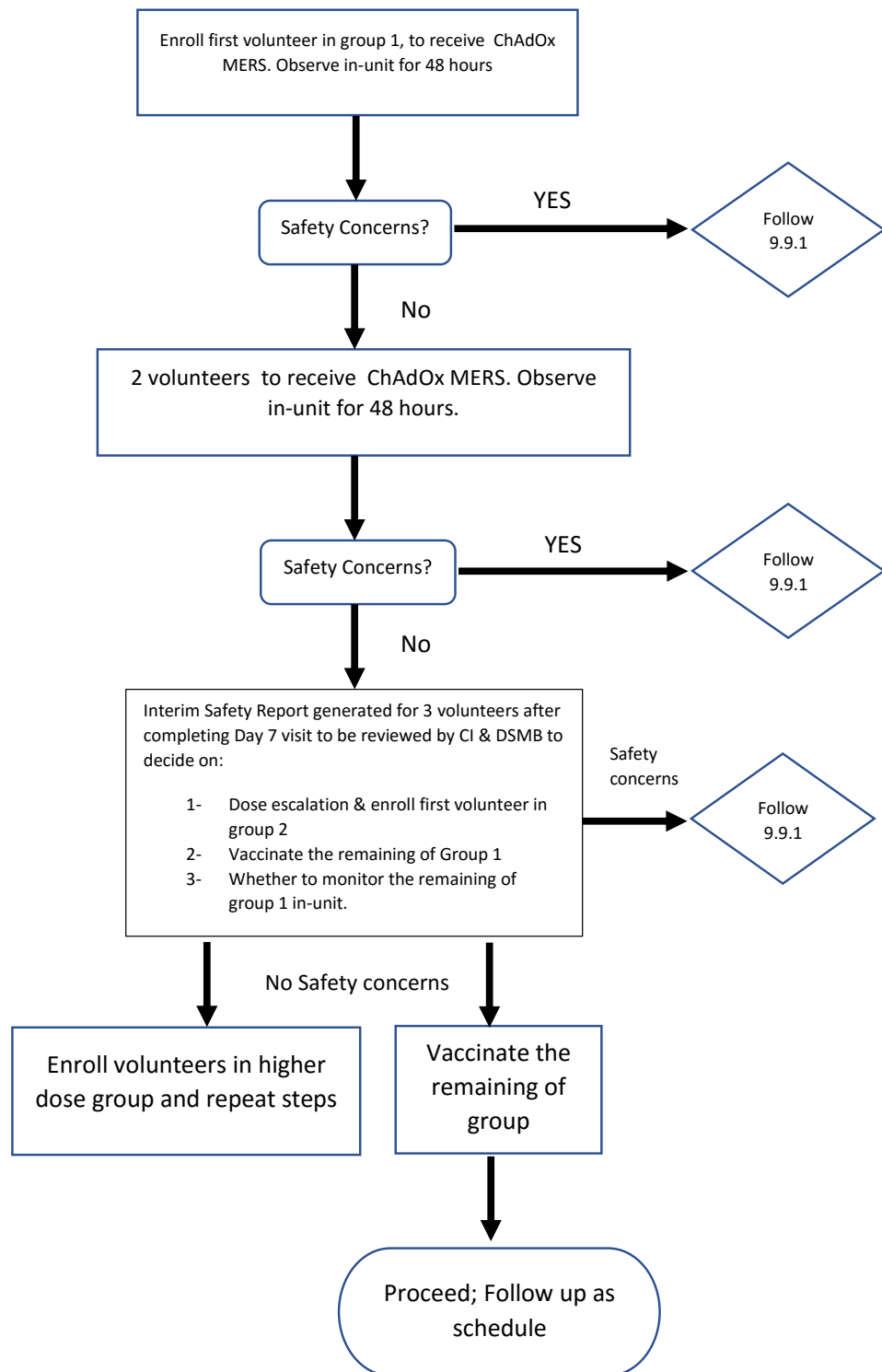
Diary cards will collect information on the timing and severity of the following solicited AEs:

Table 3. Solicited AEs as collected on post vaccination diary cards

Local solicited AEs	Systemic solicited AEs
Pain	Fever
Redness	Feverishness
Warmth	Joint pains
Itch	Muscle pains
	Fatigue
	Headache
	Nausea
	Malaise

Volunteers will be instructed on how to self-assess the severity of these AEs by the PI or their designee. There will also be space on the diary card to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms.

7.4.2.2 Sequence of Enrolment and Vaccination of Volunteers



For safety reasons, the first volunteer in Group 1 will be vaccinated ahead of any other volunteers and the profile of adverse events will be reviewed after 48 hours post vaccination. Provided there are no safety concerns, as assessed by the CI and the DSMB, another 2 volunteers will be vaccinated at the same dose after at least 48 hours has elapsed

following the first volunteer being vaccinated and at least 1 hour apart from each other. An independent safety review will be conducted by the DSMB after vaccination of the first three volunteers. This review will include an assessment of the profile of adverse events and the results of safety blood tests at day 7 post vaccination. The CI and the DSMB will be asked to provide the decision on whether to proceed with vaccinations of the remaining participants in group 1 and the first volunteer to receive the next incremental dose in group 2 and whether if there's a need for observation in CTU. If there are no safety concerns, the remaining volunteers in Group 1 and the first volunteer in group 2 may be vaccinated.

Enrolment of the first volunteer in Group 2 will only proceed if the CI and DSMB assess the data from the first three vaccinees in Group 1 as indicating that it is safe to do so. The first subject in Group 2 will be vaccinated alone, and a 48 hour gap allowed before vaccinating further subjects in this group. Provided there are no safety concerns, as assessed by the CI and the DSMB, another 2 volunteers will be vaccinated at the same dose after at least 48 hours has elapsed following the first volunteer being vaccinated and at least 1 hour apart from each other. An independent safety review will be conducted by the DSMB after vaccination of the first three volunteers. This review will include an assessment of the profile of adverse events and the results of safety blood tests at day 7 post vaccination. The CI and the DSMB will be asked to provide the decision on whether to proceed with vaccinations of the remaining participants in group 2. If there are no safety concerns, the remaining volunteers in Group 2 and the first volunteer in group 3 may be vaccinated.

Enrolment of the first volunteer in Group 3 will only proceed if the CI and DSMB assess the data from the first three vaccinees in Group 2 as indicating that it is safe to do so. The first subject in Group 3 will be vaccinated alone, and a 48 hour gap allowed before vaccinating further subjects in this group. Provided there are no safety concerns, as assessed by the CI and the DSMB, another 2 volunteers will be vaccinated at the same dose after at least 48 hours has elapsed following the first volunteer being vaccinated and at least 1 hour apart from each other. An independent safety review will be conducted by the DSMB after vaccination of the first three volunteers. This review will include an assessment of the profile of adverse events and the results of safety blood tests at day 7 post vaccination. The CI and the DSMB will be asked to provide the decision on whether to proceed with vaccinations of the remaining participants in group 3. If there are no safety concerns, the remaining volunteers in Group 3 may be vaccinated.

For safety reasons, first volunteers in each group will be observed and monitored for 48 hours in CTU. A decision on whether to continue to monitor the remaining volunteers in-unit will be made by CI and DSMB upon reviewing the interim safety report.

7.4.3 Subsequent visits: days 2, 7, 14, 28, 56 and 182.

Follow-up visits will take place 48 hours ($\pm 24h$), 7 days (± 2 days), 14 days (± 3 days), 28 days (± 3 days), 56 days (± 7 days) and 182 (± 14 days) after vaccination. Volunteers will be

assessed for local and systemic adverse events, interim history, physical examination, review of diary cards (paper or electronic) and blood tests at these time points as detailed in the schedule of attendances. Blood will also be taken for exploratory immunology purposes. For safety reasons, the first volunteers of each group will be observed in-unit for 48 hours, therefore, day 0 (vaccination day) and day 2 visits are combined. Upon reviewing safety report of first volunteers, a decision will be made by CI and DSMB on whether to continue to observe in-unit.

If volunteers experience adverse events (laboratory or clinical), which the investigator (physician), CI and/or DSMB determine necessary for further close observation, the volunteer may be asked to report to CTU or a M-NGHA hospital for observation and further medical management under the care of the Consultant on call.

Table 4. Schedule of attendances

Visit type/ settings	OP	In-unit or OP		outpatient				
Attendance Number	1 ^S	2	3	4	5	6	7	8
Timeline** (days)	≤ 90	0	2	7	14	28	56	182
Time window (days)			±1	±2	±3	±3	±7	±14
Informed Consent	X							
Review contraindications, inclusion and exclusion criteria	X	X						
Vaccination		X						
Vital signs [^]	X	X	X	X	X	X	X	X
Ascertainment of adverse events		X	X	X	X	X	X	X
Diary cards provided		X						
Diary cards collected						X		
Medical History, Physical Examination	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Biochemistry ^{\$} , Haematology (mL)	5	5	5	5		5		
Exploratory immunology [£] (mL)		50			50	50	50	50
Urinalysis	X							
Pregnancy test /β–HCG (women only)	X	X						
HLA typing (mL)		4						
HBsAg, HCV Ab, HIV serology (mL)	5							
Blood volume per visit	10	59		5	50	55	50	50
Cumulative blood volume [%]	10	69	74	79	129	184	234	284

S = screening visit; (X) = if considered necessary ^ = Vital signs includes pulse, blood pressure and temperature; \$ = Biochemistry will include Sodium, Potassium, Urea, Creatinine, Albumin and Liver function tests. £ = Exploratory immunology includes antibodies to MERS-CoV S, ex vivo interferon-gamma ELISpot responses to MERS-CoV S

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window.

% Cumulative blood volume for the volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary.

8. INVESTIGATIONAL PRODUCTS

The following vaccinations will be given in this study:

1. ChAdOx1 MERS 5×10^9 vp
2. ChAdOx1 MERS 2.5×10^{10} vp
3. ChAdOx1 MERS 5×10^{10} vp

8.1. Manufacturing and Presentation

8.1.1 Description of ChAdOx1 MERS

ChAdOx1 MERS vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of the MERS-CoV expressed from the strong CMV IE promoter.

8.1.2. ChAdOx1 MERS formulation and packaging

ChAdOx1 MERS is manufactured in formulation buffer at a concentration of 1.74×10^{11} vp/mL. The drug product is filled into 2mL glass vials with a 13 mm grey bromobutyl rubber freeze-dry stopper (CE Marked, supplied by Adelphi Tubes) and a 13 mm aluminium seal. The nitrogen filled vials are supplied sterile. The containers and closures are tested for compliance with defined specifications. The vials are made from Ph Eur Type 1 glass.

8.2 Supply

ChAdOx1 MERS has been formulated and vialled under Good Manufacturing Practice conditions at the Clinical Biomanufacturing Facility (CBF), University of Oxford. At the CBF the vaccine will be labelled for the trial by a Qualified Person (QP) before transfer to the clinical site in Saudi Arabia.

8.3 Storage

The vaccine is stored at nominal -80°C in a locked freezer, at the clinical site. All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with APP 1429-33 **Vaccine Storage, Transport and Handling and DPP 9839/CR/D05V01 Translational Research Unit Pharmacy..**

8.4 Administration of Investigational Medicinal Products

On vaccination day, ChAdOx1 MERS will be allowed to thaw at room temperature and will be administered within 1 hour of removal from the freezer. The vaccine will be administered intramuscularly into the deltoid of the non-dominant arm (preferably). All volunteers will be observed in the unit for 1 hour (± 10 minutes) after vaccination, then moved to the inpatient

CTU ward for 48 hours. During administration of the investigational products, Advanced Life Support drugs and resuscitation equipment will be immediately available for the management of anaphylaxis. Vaccination will be performed and the IMPs handled according to guidelines described in Appendix 1.

8.5 Minimising environmental contamination with genetically modified organisms (GMO)

The study will be performed in accordance with the Saudi FDA regulations. In order to minimise dissemination of the recombinant vectored vaccine virus into the environment, inoculation sites will be covered with a dressing after immunisation. This should absorb any virus that may leak out through the needle track. The dressing will be removed from the injection site after 30 minutes (+15/- 5 minutes) and will be disposed as a biohazard waste by autoclaving. Any vaccine spillage incidents will be covered with a dressing to absorb the spilled liquid and will be disposed as a biohazard waste by autoclaving.

9. ASSESSMENT OF SAFETY

Safety will be assessed by the frequency, incidence and nature of adverse events and serious adverse events arising during the study.

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a volunteer, which may occur during or after administration of an Investigational Medicinal Product (IMP) and does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study intervention, whether or not considered related to the study intervention.

9.1.2 Adverse Reaction (AR)

An AR is any untoward or unintended response to an IMP. This means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting medical Investigator as having a reasonable suspected causal relationship to an IMP (i.e. possibly, probably or definitely related to an IMP) will qualify as adverse reactions.

9.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IMP).

9.1.4 Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following outcomes, whether or not considered related to the study intervention.

- Death
- Life-threatening event (i.e., the volunteer was, in the view of the Investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity (i.e., substantial disruption of one's ability to carry out normal life functions).
- Hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.

- An important medical event (that may not cause death, be life threatening, or require hospitalisation) that may, based upon appropriate medical judgment, jeopardise the volunteer and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.
- Congenital anomaly or birth defect.

9.1.5 Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

9.1.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB or Summary of Product Characteristics (SmPC).

9.2 Foreseeable Adverse Reactions:

The foreseeable ARs following vaccination with ChAdOx1 MERS include injection site pain, erythema, warmth, swelling, pruritus, myalgia, arthralgia, headache, fatigue, fever, feverishness, malaise and nausea.

9.3 Expected Serious Adverse Events

No serious adverse events are expected in this study.

9.4 Causality Assessment

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the CI-delegated clinician. An intervention-related AE refers to an AE for which there is a probable or definite relationship to administration of a vaccine. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy (Table 5). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (e.g. if a holding or stopping rule is activated) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator. In

order to reduce potential bias in collected AE data, all AEs (excluding SAEs) for which causality has been assigned will be reviewed by an independent clinician who will assign causality separately to the lead trial clinician. Any discrepancies in the assigned causality scores should be discussed between the lead clinician and independent clinician so that an agreed causality can be assigned. This agreed causality should be used for the data analysis.

Table 5. Guidelines for assessing the relationship of vaccine administration to an AE.

0	No Relationship	No temporal relationship to study product and Alternate aetiology (clinical state, environmental or other interventions); and Does not follow known pattern of response to study product
1	Unlikely	Unlikely temporal relationship to study product and Alternate aetiology likely (clinical state, environmental or other interventions) and Does not follow known typical or plausible pattern of response to study product.
2	Possible	Reasonable temporal relationship to study product; or Event not readily produced by clinical state, environmental or other interventions; or Similar pattern of response to that seen with other vaccines
3	Probable	Reasonable temporal relationship to study product; and Event not readily produced by clinical state, environment, or other interventions or Known pattern of response seen with other vaccines
4	Definite	Reasonable temporal relationship to study product; and Event not readily produced by clinical state, environment, or other interventions; and Known pattern of response seen with other vaccines

9.5 Reporting Procedures for All Adverse Events

All local and systemic AEs occurring in the 28 days following each vaccination observed by the investigator or reported by the volunteer, whether or not attributed to study medication, will be recorded (excluding those expected consequences from venepuncture, described in section 5.3). Data will be collected from volunteers' diaries and from scheduled visits and blood tests. AE reports will be generated upon interim safety review (for the first 3 volunteers of each group) and whenever required by regulatory authority (SFDA). CI must be immediately notified once investigator becomes aware of any grade 3 AE (including lab

values). All AEs that result in a volunteer's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the volunteer consents to this). Serious adverse events (SAEs) will be collected throughout the entire trial period.

9.5.1 Reporting Procedures for Serious AEs (See SOP 406, "AE Management/ APP 1433-37 Conducting Research Studies" and APP 1435-08: Safety Reporting System (SRS))

In order to comply with current regulations on serious adverse event reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported on the SAE forms to members of the study team immediately, so the investigators become aware of their occurrence, as described in the above-mentioned SOP and APPs. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The Data and safety management board (DSMB) will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the DSMB will be notified immediately (within 24 hours) of the Investigators' being aware of their occurrence. SAEs will be reported to the ethical committee (IRB) immediately and within twenty-four (24) hours of discovering the event through the electronic Safety Reporting System (SRS) followed by a detailed follow-up report within 7 calendar days as described in the above-mentioned SOP. In addition to the expedited reporting above, the Investigator shall include all SAEs in the annual Development Safety Update Report (DSUR) report.

9.5.2 Reporting Procedures for SUSARS

The Chief Investigator will report all SUSARs to the SFDA and ethical committee (M-NGHA IRB) within required timelines (15 days for all SUSARs, unless life threatening in which case 7 days, with a final report within a further 8 days (total 15). The Chief Investigator will also inform all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants. All SUSARs and deaths occurring during the study will be reported to the Sponsor. For all deaths, available autopsy reports and relevant medical reports will be made available for reporting to the relevant authorities.

9.5.3 Development Safety Update Report

A Development Safety Update Report (DSUR) will be submitted by the Sponsor to the competent authority (SFDA) and ethical committee (IRB) on the anniversary of the first approval date from the regulatory authority for each IMP.

9.6 Assessment of severity

The severity of clinical and laboratory adverse events will be assessed according to the scales in Tables 6-10..

Table 6. Severity grading criteria for local adverse events.

Adverse Event	Grade	Intensity
Erythema at injection site*	1	>3 - ≤50 mm
	2	>50 - ≤100 mm
	3	>100 mm
Swelling at injection site	1	>3 - ≤20 mm
	2	>20 - ≤50 mm
	3	>50 mm
Ulceration/necrosis of skin at injection site	1	None
	2	None
	3	Any

*erythema or swelling ≤3mm is an expected consequence of skin puncture and will therefore not be considered an adverse event. Marked redness or swelling or any skin ulceration should also be documented by photograph with a size indicator, as long as the volunteer has consented for this. Photographs should be stored in the 'Investigator comments' section of the participants' paper CRF

Table 7. Severity grading criteria for physical observations

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Fever (oral)	37.6°C - 38.0°C	38.1°C – 39.0°C	>39.0°C
Tachycardia (bpm)*	101 - 115	116 – 130	>130
Bradycardia (bpm)**	50 – 54	40 – 49	<40
Systolic hypertension (mmHg)	141 - 159	160 – 179	≥180
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80
Diastolic hypertension (mmHg)	91 - 99	100 – 109	≥110

*Taken after ≥10 minutes at rest

**Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes.

***Only if symptomatic (e.g. dizzy/ light-headed)

Table 8. Severity grading criteria for local and systemic AEs.

GRADE 0	None: Symptom not experienced
GRADE 1	Mild: Short-lived or mild symptoms; medication may be required. No limitation to usual activity
GRADE 2	Moderate: Mild to moderate limitation in usual activity. Medication may be required.
GRADE 3	Severe: Considerable limitation in activity. Medication or medical attention required.

Table 9. Severity grading criteria for haematology lab values

Routine hematology			Lab range	Grade 0	Grade 1	Grade 2	Grade 3
Hemoglobin	Male	g/l	135-180	126 - 170	115 - 125	100 - 114	<100
	Female		120-160	114 - 150	105 - 113	90 - 104	<90
White blood cells	Elevated	10^9/L	4-11	3.51 - 11.49	11.50 -15.00	15.01 - 20.00	>20
	Low				2.50 - 3.50	1.50 - 2.49	<1.50
Platelets		10^9/L	150-400	136 - 400	125 - 135	100 - 124	<100
Neutrophils		10^9/L	2 - 7.5	1.5 - 7.5	1.00 - 1.49	0.50 - 0.99	<0.50
Lymphocytes		10^9/L	1 - 4.4	1 - 4.4	0.75 - 0.99	0.50 - 0.74	<0.50
Eosinophils		10^9/L	0.1-0.7	0.0 - 0.64	0.65 - 1.50	1.51 - 5.00	>5.00

Table 10. Severity grading criteria for biochemistry lab values

Routine Biochemistry		Lab range	Grade 0	Grade 1	Grade 2	Grade 3
Sodium	Elevated	mmol/l	136-145	147 - 148	149 - 150	>150
	Low		135 - 146	132 - 134	130 - 131	<130

Potassium	Elevated	mmol/l	3.5 -5.1	3.4 - 5.0	5.1 – 5.2	5.3 – 5.4	>5.4
	Low				3.2 – 3.3	3.0 – 3.1	<3.0
BUN		mmol/l	2.5 -6.7	2.5 - 8.1	8.2 – 8.9	9.0 – 11.0	>11.0
Creatinine		μmol/l	50-98 F 64-110 M	49 - 113	114 -156	157 - 312	>312
Bilirubin	Normal LFT	μmol/l	3.4 – 20.5	0 - 26	27 - 31	32-42	>42
Bilirubin	Abnormal LFT	μmol/l	3.4 – 20.5	0 - 22	23 - 26	27 - 31	>31
ALT		U/l	5 - 55	5 - 55	56 - 112	113 - 225	>225
AST		U/l	5-34	5 - 51	52 - 105	106 -210	>210
Alk Ph		U/l	40-150	30 - 142	143 - 260	261 - 390	>390
Albumin		g/l	35- 50	32 - 50	28 - 31	25 - 27	<25

9.7 Procedures to be followed in the event of abnormal findings

Laboratory parameters for inclusion/exclusion in the trial will be considered on an individual basis, with investigator discretion for interpretation of results and the need for repeated tests. Laboratory adverse events will be assessed using the tables 9 and 10. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator.

9.8 Data and Safety Management Board

A Data and Safety Management board (DSMB) will be appointed to provide real-time safety oversight. The DSMB will review SAEs deemed possibly, probably or definitely related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being

aware of their occurrence. The DSMB has the power to place the study on hold if deemed necessary following a study intervention-related SAE. There will be a minimum of two other appropriately qualified committee members. All correspondence between Investigator and DSMB will be conveyed by the Investigator to the trial Sponsor.

The chair of the DSMB may be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:

- Following any SAE deemed to be possibly, probably, or definitely related to a study intervention.
- Any other situation where the Investigator, the IRB or trial Sponsor feels independent advice or review is important.

9.8.1 Interim Safety Reviews

Interim safety reviews with the Chairman of the DSMB are scheduled during the enrolment of the first volunteers in each group and prior to dose escalations, as outlined in section 7.4.2.2.

The safety profile of the IMP will be assessed on an on-going basis by the Investigators with communication to the DSMB as necessary. The Chief Investigator and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise.

9.9 Safety Stopping/Holding Rules

Safety holding rules have been developed considering the fact that this is a phase 1b dose escalation study.

‘Solicited adverse events’ are those listed as foreseeable adverse events in table 3 in section 7.4.2.1 of the protocol, occurring within the first 7 days after vaccination (day of vaccination and six subsequent days). ‘Unsolicited adverse events’ are adverse events other than the foreseeable AEs occurring within the first 7 days, or any AEs occurring after the first 7 days after vaccination.

9.9.1 Group holding rules

For safety reasons the first volunteer to receive a new vaccine dose in Groups 1, 2 and 3 will be vaccinated alone and we will wait 48 hours before vaccinating subsequent volunteers. Two further volunteers may be vaccinated 48 hours after the first, and then at least another 48 hours gap will be left before vaccinating the rest of the volunteers receiving the same dose of the vaccine.

- **Solicited local adverse events:**
 - If 2 or more vaccinations in a group are followed by the same Grade 3 solicited local adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >48 hrs.

- **Solicited systemic adverse events:**
 - If 2 or more vaccinations in a group are followed by the same Grade 3 solicited systemic adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >48 hrs.
- **Unsolicited adverse events:**
 - If 2 or more vaccinations in a group are followed by the same Grade 3 unsolicited adverse event (including the same laboratory adverse event) that is considered possibly, probably or definitely related to vaccination and persists at Grade 3 for > 48hrs.
- **A serious adverse event considered possibly, probably or definitely related to vaccination occurs**
- **Death occurs**
- **A life-threatening reaction occurs**

If a holding rule has been met and following an internal safety review it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data must be submitted to the regulatory authority as a request for a substantial amendment. The internal safety review will consider:

- The relationship of the AE or SAE to the vaccine.
- The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.
- If appropriate, additional screening or laboratory testing for other volunteers to identify those who may develop similar symptoms and alterations to the current Participant Information Sheet (PIS) are discussed.
- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The local ethics committee and vaccine manufacturers will also be notified if a holding rule is activated or released.

As per section 6.3.5, if a volunteer has an acute illness (moderate or severe illness with or without fever) or a fever (oral temperature greater than 37.5°C) at the scheduled time of administration of investigational product, the volunteer will not receive the vaccine at that time. The vaccine may be administered to that volunteer at a later date within the time window specified in the protocol (see Table 4) or they may be withdrawn from the study at the discretion of the Investigator.

All vaccinated volunteers will be followed for safety until the end of their planned participation in the study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

In addition to these pre-defined criteria, the study can be put on hold upon advice of the Local Safety Monitor, Chief Investigator, Study Sponsor, Regulatory Authority, Ethical Committee (IRB) or Local Safety Committee, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the volunteers or the reliability of the data.

10. STATISTICS

Data will be presented by patient and summarized by dose level and overall, Only dose groups that enrolled at least 1 patient will be presented. Tabulations will be produced for safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

The analysis of primary endpoint will be conducted using the Safety Population (All patients who received at least 1 dose of study treatment), and presented by dose level and overall. Safety data will be analysed using descriptive statistics and tabulation. No formal statistical comparisons are planned. All safety data will be presented in listings.

The immunogenicity parameters will be summarized by dose level and overall for each time point. We will assess vaccine immunogenicity by comparing the change in these immunological parameters from baseline to different time points using Generalized linear models (GLM) for repeated measures. Patient profile plot will also be generated by dose levels. All immunogenicity patients data will be listed by dose levels and overall.

Sample Size Selection

This is a descriptive phase Ib trial in ME volunteers that will balance the safety of volunteers with the aims to assess the vaccine's safety profile and immunogenicity after selected doses of the vaccines. The primary dose comparison will be between Groups 1, 2 and 3, which will have 6-9 subjects each. MERS-CoV S-specific immunogenicity will be the key immunological readout assessed by a variety of immunological assays.

11. DATA MANAGEMENT

11.1 Data Handling

The Chief Investigator will be responsible for all data that accrues from the study. The data will be entered into the volunteers' CRFs in a paper and/or electronic format (using OpenClinica™ database). Electronic data will be stored on secure servers which are outsourced by OpenClinica™. Data will be entered in a web browser on PCs in the TRU and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets American FDA part 11B standards. This includes safety data, laboratory data (both clinical and immunological) and outcome data.

Adverse event data will also be entered onto electronic or paper diaries by the volunteer

11.2 Record Keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory (e.g. SFDA) and institutional (i.e. IRB) requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s), as well as ethical and regulatory teams to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

11.3 Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the CRF. Source documents are original documents, data, and records from which the volunteer's CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, laboratory records, diaries, and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, adverse event data and details of vaccinations. All source data and volunteer CRFs will be stored securely.

11.4 Data Protection

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

11.5 Data Quality

Data collection tools will undergo appropriate validation to ensure that data is collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs (APP 1433-37 Conducting Research studies; 501 DM “clinic data management” and 502 DM “Use of electronic data Management Systems”. If additional, study specific information is required, an approved Data Management Plan will be implemented.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

12.1 Investigator procedures

Approved site-specific standard operating procedures (SOPs), from KAIMRC and Oxford, will be used at all clinical and laboratory sites.

12.2 Monitoring

Monitoring will be performed according to ICH GCP, APP 1432-20 Monitoring Research Studies and SOP 305 PM Monitoring Visit / APP 1433-37 Conducting Research Studies . As KAIMRC is the sponsor, KAIMRC will identify a monitoring team whether from KAIMRC or external. Following written plan (see Appendix 2), the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities such as SFDA.

12.3 Protocol deviation (see DPP 9812/AR/D07V01 Regulatory Requirements for Conducting Phase 1 Clinical Trials)

Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. Each deviation will be assessed as to its impact on volunteer safety and study conduct. Significant deviations will be listed in the end of study report.

12.4 Audit & inspection

The QA manager conducts systems based internal audits to check that trials are being conducted according to local procedures and in compliance with GCP and applicable regulations.

The Sponsor, trial sites, and IRB may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations.

GCP inspections may also be undertaken by the SFDA to ensure compliance with protocol and the SFDA Clinical Trials Regulations. The Sponsor will assist in any inspections and will support the response to the SFDA as part of the inspection procedure.

13. SERIOUS BREACHES

In the UK, the Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach. In this trial the Sponsor (KAIMRC) will comply with the SDFA clinical trials regulations and will notify any "serious breaches" to the SFDA.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor will be informed within one working day.

14. ETHICS AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

The Investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki.

14.2 Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in full conformity with the Good Clinical Practice (GCP).

14.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the M-NGHA IRB for their written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

No substantial amendments to this protocol will be made without consultation with, and agreement of, the Sponsor. Any substantial amendments to the trial that appear necessary during the course of the trial must be discussed by the Investigator and Sponsor concurrently. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Chief Investigator and will be made a formal part of the protocol following ethical and regulatory approval.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory (SFDA) and ethical committee (IRB) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject.

14.4 Volunteer Confidentiality

All data will be anonymised: volunteer data will be identified by a unique study number in the CRF and database. A separate confidential file containing identifiable information will be stored in a secured location in accordance with M-NGHA data protection policies. Only the Sponsor representative, Investigators, the clinical monitor, the IRB and the SFDA will have access to the records. PI will provide the IRB with volunteers medical record number/subject ID upon recruiting and deemed eligible for enrolment. Blood samples taken during the trial fall into two categories; routine blood test (haematology, chemistry) will be sent to diagnostic lab in the hospital and will be identified in BestCare (Health Information System) as a record number in case lab results are needed. In addition to routine tests, samples will also be sent to the infectious Disease research lab for the purpose of the research study (exploratory immunology); blood will be drawn into coded blood tubes where each research

subject will be given a specific barcode arranged through the research coordinator, the records of the match between the subject and both the barcode and BestCare record number will be kept by the research coordinator and only accessed by the Principle investigator and the Co-Investigators. Photographs taken of vaccination sites (if required, with the volunteer's written, informed consent) will not include the volunteer's face and will be identified by the date, trial code and subject's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

15. FINANCING AND INSURANCE

15.1 Financing

The study is funded by the UK Department of Health

15.2 Insurance

The M-NGHA has eligibility policy in place which would cover and operate in the event of any participant suffering harm as a result of their involvement in the research. Therefore, volunteers will have to have M-NGHA eligibility before they are enrolled in the study. Volunteers will be issued Referral Letters (RL) in accordance with *APP 1433-40, Determining Eligibility for Medical Care & Admission*

15.3 Compensation

Volunteers will be compensated for their time and for the inconvenience caused by procedures. They will be compensated 250 SAR for attending the screening visit. For all other trial visits as outlined in Table 4, compensation will be calculated according to the following:

- Travel expenses:
 - 100 SAR per visit. Where travel expenses are greater than 100 SAR per visit because the volunteer lives outside the city of the trial site, the volunteer will be given further reimbursement to meet the cost of travel necessary for study visits.
- Inconvenience of blood tests:
 - 100 SAR per blood donation
- Time required for visit:
 - 200 SAR per hour OR in case of in-unit observation, 2500 SAR per stay.

16. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Data from the study may also be used as part of a thesis for a PhD or MD.

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APPENDIX 1: ChAdOx1 Study – Vaccine Administration

Version: 1

Date: August 2, 2018

1. INTRODUCTION

These guidelines are to be followed during preparation and administration of study vaccine in ChAdOx1 MERS Clinical Trial.

2. GENERAL CONSIDERATIONS

2.1 These guidelines are established to maintain a safe environment for both vaccinees and staff by:

- 2.1.1** minimizing the possibility of vaccines being administered to the wrong patient
- 2.1.2** minimizing the possibility of incorrect vaccines being administered
- 2.1.3** minimizing the possibility of an incorrect amount of vaccine being administered
- 2.1.4** minimizing the possibility of an out of date vaccine being administered
- 2.1.5** ensuring vaccines are administered in a safe, appropriate and consistent manner.

2.2 Doctors and nurses providing immunizations are professionally accountable for this work, as defined by their professional bodies.

2.3 All healthcare professionals ordering or administering vaccines must have received adequate training in immunization, including the recognition and treatment of anaphylaxis. They should maintain and update their professional knowledge and skills through appropriate training

2.4 All staff delegated to perform vaccination must be familiar with, and trained in, these SOPs ensuring that they are competent and trained to do so.

3. HAZARDS & PRECAUTIONS

3.1 GMO

3.2 Sharp injuries

4. EQUIPMENT & MATERIALS

4.1 Clean procedure trolley

4.2 Sharps bin

4.3 Autoclave waste bag

- 4.4 Personal Protective Equipment (PPE): gloves, apron, eye protection and face mask.
- 4.5 Needles/syringes as appropriate
- 4.6 Alcohol skin swabs
- 4.7 Occlusive dressing
- 4.8 Access to spill kit

5. PROCEDURES

5.1 Preparation:

- 5.1.1 The vaccine will be prepared for administration in the clinical trial unit CTU.
- 5.1.2 Ensure that the room for administration is adequately prepared, including life support equipment, equipment to handle spillage, and a plastic chair for use by the volunteer when being vaccinated.
- 5.1.3 Confirm the volunteer's identity on arrival by crosschecking their name and date of birth with the information in the CRF and/or ID, if applicable.
- 5.1.4 Carry out all pre-vaccination procedures as detailed in the protocol. Inform the volunteer of the nature, route of administration (if used, blinding rules must be maintained), of possible side effects and give the opportunity to ask questions and even withdraw consent (if so desired).
- 5.1.5 Collect the vaccine. Two members of staff must collect the vaccine. The person removing and handling the vaccine must wear gloves. Identify the vaccine required from the details provided in the CRF, ensure the vaccine log is available, remove the vaccine from storage, check and record all details against the CRF and log. Place the vial in an appropriate transport tube for transport to the clinic room. Repeat this process for each vaccine required.
- 5.1.6 **Record the following details from the vaccine directly from the vial label in to the log:**
 - 5.1.6.1 Date and time of removal
 - 5.1.6.2 Trial number
 - 5.1.6.3 Product name
 - 5.1.6.4 Batch
 - 5.1.6.5 Vial number
 - 5.1.6.6 Expiry date
 - 5.1.6.7 Volunteer's ID number
 - 5.1.6.8 Stock level remaining
 - 5.1.6.9 Log to be signed by two members of staff at the time of checking
- 5.1.7 Once returned to the clinical area, place the vaccine on the injection tray on top of the procedure trolley. Wear a disposable apron, clean gloves and protective eyewear.
- 5.1.8 Hold the unopened vial in the gloved hand to encourage thawing of the frozen vaccine. Once defrosted, remove the cap and swab the septum (bung) using an alcohol wipe, allow to dry.

- 5.1.9** Prior to inserting the needle into the vial, ensure all possible air is expelled from the syringe; air being forced into the vial may cause a build-up of pressure and result in ejection of its content when withdrawing the needle.
- 5.1.10** Where very small volumes are being used it is likely that air bubbles will appear in the syringe. By keeping the vial on the needle, it will be possible to remove these by tapping the syringe and drawing back and forth, AT NO TIME SHOULD THE NEEDLE BE REMOVED FROM THE VIAL AND “FLICKED” AS THIS MAY LEAD TO ENVIRONMENTAL CONTAMINATION WITH A GMO. If air bubbles are a problem hold the vial between the thumb and forefinger and syringe with the other fingers and gently flick the barrel of the syringe with the other hand.
- 5.1.11** Once the required volume is drawn (see below, Vaccine Dilution), recheck the vaccine label (two members of the clinical team) against the vaccination administration record and enter all information as required (i.e. the trial number, product name, concentration, batch, expiry date, dose to be given and volume) into the CRF.
- 5.1.12** Administer the vaccine as described below. Note that there is a maximum of 60 minutes from collecting the vaccine to administration.
- 5.1.13** Once the vaccine has been administered, record the time of injection (using the clock in the clinic room and 24-hour format). Remove the flag label from the vial, annotate with the volunteer’s ID number and stick to the vaccination administration record.

5.2 Vaccine Dilution Group 1(5×10^9 vp):

5.2.1 Calculations:

GROUP 1		
(A) To prepare dilution of ChAdOx1 MERS vaccine in volume of	A=	1000μl
(B) Dilution required	B=	1/10
(C) Volume of neat ChAdOx1 MERS vaccine required (B x A)	C=	100μl
(D) Volume of diluent required 1ml – (B x A)	D=	900μl
(E) Product concentration in original vial	E=	1.74×10^{11} vp/ml
(F) Final concentration after dilution of (E x B)	F=	1.74×10^{10} vp/ml
(G) Intended dose for administration	G=	5×10^9 vp
(H) Volume to be extracted (G/F)1000	H=	290μl
Calculation reviewed by oxford trial MERS001 team and rechecked by: Dr. Sultan Almaziad (Clinician) and Ms. Rawan Alanazi (Research Pharmacist), and Ms. Badriah Almutairi (Research Coordinator)		

5.2.2 Equipment

- 1 x vial ChAdOx1 MERS
- 1 x 2ml Adelphi vial or similar for dilution and mixing
- 1 x 0.9% saline for injection (5 or 10ml)
- 1 x 0.5ml insulin syringe with 29g needle attached (NB.1ml may be used if not readily available)
- 1 x 1ml insulin syringe with 29g needle attached
- 1 x BD 1ml plastipac syringe
- 1 x 23g needle (3/4") Blue
- 2 x alcohol swab
- PPE – Gloves, apron, goggles
- Sharps bin
- Treatment room trolley (clean)

5.2.3 Preparation

- Collect and prepare equipment, PPE and work surface.
- Record all details on the administration record sheet.
- Collect vaccines and defrost as required.
- Gently swirl the vial (do not shake) to ensure even suspension of vaccine within the vial.
- Remove safety caps from both vaccine vial and a mixing vial.
- Clean the top of each vial with an alcohol swab – allow drying.

5.2.4 Dilution to 1:10 solution

- Using the 0.5ml insulin syringe/needle, draw up 100 μ l ChAdOx1 MERS vaccine (≈ 10 units on the syringe).

2. With the Adelphi vial sitting on the work surface and using a single depression of the syringe, slowly and gently inject the 100µl of ChAdOx1 MERS vaccine into this vial. Remove and dispose of the needle/syringe.
3. Using the 1ml insulin syringe draw up 900µl of 0.9% saline (\approx 90 units on the syringe).
4. Inject the 900 µl of saline into the Adelphi vial containing the 100µl of ChAdOx1 MERS vaccine.
5. Remove and dispose of the syringe/needle and gently swirl the vial to aid mixing.

5.2.5 Drawing up required volume for injection

1. Using a 1ml syringe and 23g, 1 ¼" needle. Insert the needle into the vial and invert
2. Gently draw back and reinject the diluted vaccine three times to ensure a good mix (do not remove the needle from the vial during this process).
3. Draw up a volume of 290µl, ensuring the syringe/needle are filled.
4. Leave the needle in the vial until ready to administer the vaccine.
5. Administer in accordance with the protocol into the deltoid of the non-dominant arm as described below
6. Dispose of all equipment safely in suitable containers prior to autoclaving.

5.3 Vaccine Dilution Group 2 (2.5×10^{10} vp):

5.3.1 Calculations:

GROUP 2		
(A) To prepare dilution of ChAdOx1 MERS vaccine in volume of	A=	630μl
(B) Dilution required	B=	1/3
(C) Volume of neat ChAdOx1 MERS vaccine required (B x A)	C=	210μl
(D) Volume of diluent required 1ml – (B x A)	D=	420μl
(E) Product concentration in original vial	E=	1.74x10¹¹ vp/ml
(F) Final concentration after dilution of (E x B)	F=	5.8 x10¹⁰ vp/ml
(G) Intended dose for administration	G=	2.5 x10¹⁰ vp
(H) Volume to be extracted (G/F)1000	H=	430μl
Calculation reviewed by oxford team and rechecked by: Dr. Sultan Almaziad (Clinician) and Ms. Rawan Alanazi (Research Pharmacist), and Ms. Badriah Almutairi (Research Coordinator)		

5.3.2 Equipment

- 1 x vial ChAdOx1 MERS
- 1 x 2ml Adelphi vial or similar for dilution and mixing
- 1 x 0.9% saline for injection (5 or 10ml)
- 2 x 0.5ml insulin syringe with 29g needle attached (NB.1ml may be used if not readily available)
- 1 x BD 1ml plastipac syringe
- 1 x 23g needle (3/4") Blue
- 2 x alcohol swab
- PPE – Gloves, apron, goggles
- Sharps bin
- Treatment room trolley (clean)

5.3.3 Preparation

1. Collect and prepare equipment, PPE and work surface.
2. Record all details on the administration record sheet.
3. Collect vaccines and defrost as required.
4. Gently swirl the vial (do not shake) to ensure even suspension of vaccine within the vial.
5. Remove safety caps from both vaccine vial and a mixing vial.
6. Clean the top of each vial with an alcohol swab – allow drying.

5.3.4 Dilution to 1:3 solution

1. Using the 0.5ml insulin syringe/needle, draw up **210 μ l** ChAdOx1 MERS vaccine (\approx 21 units on the syringe).

2. With the Adelphi vial sitting on the work surface and using a single depression of the syringe, slowly and gently inject the 210µl of ChAdOx1 MERS vaccine into this vial. Remove and dispose of the needle/syringe.
3. Using the 0.5ml insulin syringe draw up **420µl** of 0.9% saline (\approx 42 units on the syringe).
4. Inject the 420µl of saline into the Adelphi vial containing the 210µl of ChAdOx1 MERS vaccine.
5. Remove and dispose of the syringe/needle and gently swirl the vial to aid mixing.

5.3.5 Drawing up required volume for injection

1. Using a 1ml syringe and 23g, 1 ¼" needle. Insert the needle into the vial and invert
2. Gently draw back and reinject the diluted vaccine three times to ensure a good mix (do not remove the needle from the vial during this process).
3. Draw up a volume of 430µl, ensuring the syringe/needle are filled.
4. Leave the needle in the vial until ready to administer the vaccine.
5. Administer in accordance with the protocol into the deltoid of the non-dominant arm as described below
6. Dispose of all equipment safely in suitable containers prior to autoclaving.

5.4 Vaccine Dilution Group 3:

5.4.1 Calculations:

GROUP 3		
(A) Product concentration in original vial	A=	1.74×10^{11} vp/ml
(B) Intended dose for administration	B=	5×10^{10} vp
(C) Volume to be extracted (B/A)1000	C=	290µl
Calculation reviewed by oxford team and rechecked by: Dr. Sultan Almaziad (Clinician) and Ms. Rawan Alanazi (Research Pharmacist), and Ms. Badriah Almutairi (Research Coordinator)		

5.4.2 Equipment

- 2 x vial ChAdOx1 MERS
- 1 x BD 1ml plastipac syringe
- 1 x 23g needle (3/4") Blue
- 2 x alcohol swab
- PPE – Gloves, apron, goggles
- Sharps bin
- Treatment room trolley (clean)

5.4.3 Preparation

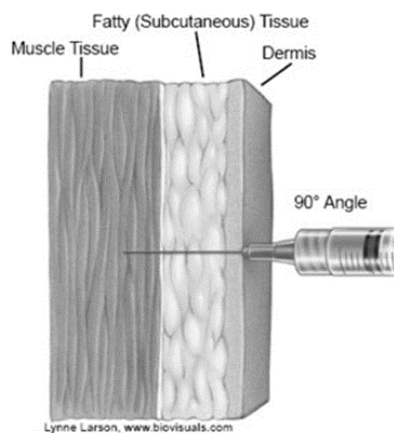
- Collect and prepare equipment, PPE and work surface.
- Record all details on the administration record sheet.
- Collect vaccines and defrost as required.
- Gently swirl the vial (do not shake) to ensure even suspension of vaccine within the vial.
- Remove safety caps from both vaccine vial and a mixing vial.
- Clean the top of each vial with an alcohol swab – allow drying.

5.4.4 Drawing up required volume for injection

- Using a 1ml syringe and 23g, 1 ¼" needle and ensuring both the hub of the needle and needle are filled, draw up a total of 290 µl from the two ChAdOx1 MERS vials.
- Leave the needle in the vial until ready to administer the vaccine.
- Administer in accordance with the protocol into the deltoid of the non-dominant arm as described below
- Dispose of all equipment safely in suitable containers prior to autoclaving.

5.5 Intramuscular (IM) administration of vaccines

- 5.5.1** The Volunteers are to be sitting during the procedure on a chair which can be washed down in case of spills.
- 5.5.2** Deltoid:
 - 5.5.2.1** The deltoid site can be found by identifying the acromial process and the point on the lateral arm in line with the axilla.
 - 5.5.2.2** IM injection should be the non-dominant arm.
 - 5.5.2.3** Vaccinees should be asked to expose the deltoid region and rest their hand on their hip to allow for greater muscle relaxation.
 - 5.5.2.4** Spread the skin taut and insert the needle about 2.5cm below the acromial process at 90°. The radial nerve and the brachial artery must be avoided.



5.6 Disposal

- 5.6.1** Any vaccine spillage incidents will be covered with a dressing to absorb the spilled liquid and will be disposed as a biohazard waste by autoclaving.
- 5.6.2** Place all equipment used in the administration of GMO products, including the dressing, gloves and apron in the appropriate waste receptacles, and autoclave prior to disposal into the clinical waste system, in accordance with APP 1430-46 and ICM-IX-02; Waste Management.

Appendix 2: Monitoring Plan

Purpose

The purpose of the Monitoring Plan is to facilitate compliance with GCP guidelines, KAIMRC requirements and other applicable authorities' regulations, which require the Monitor to verify that:

- The rights and well-being of human subjects are protected
- Reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with currently approved protocol, GCP guidelines and applicable regulatory requirements.

This document identifies key monitoring activities, the type and nature of data to be reviewed over the course of the research study.

Site Visit Confirmation

The study team will communicate with the monitoring unit in order to confirm a date and time for the Site Initiation Visit. Its will be determined based on the recruitment rate.

Study Staff Responsibilities and Training

(Specify any protocol specific training and delegation of responsibilities for study staff based on their role)

Staff Responsibilities will be specified in the delegation log.

Staff Training:

Oxford Training

Protocol Training

OpenClinica Training.

Frequency of Visits and Monitoring Activities

The Monitoring Unit will provide monitoring before, during and at the end of research studies.

In general, monitoring visits will be scheduled based on recruitment rate and safety review points, the study team will communicate with the monitors and request a visit when needed, however the monitors must be present in ,**but not limited to**, the below situations.

- Prior to enrolling the first subject and after IRB approval
- During the enrollment visit of the first subject. Enrollment.
- Whenever the study team request a visit based on safety review points and recruitment rate.
- After the last subject has completed their participation in the study.

(Specify the frequency of monitoring visits for this research study)

The monitoring schedules for any specific research study may be revised, based on and not limited to the following reasons: (will attach it)

- History of serious adverse events/reports generated from the study
- Where a history of protocol deviations suggests non-compliance with the protocol.
- Complexity of the research study
- Subject enrollment rate
- IRB and/or research office request.

(Indicate who will be responsible for conducting monitoring visits)

Extent of Data Monitoring

(Indicate the extent of data monitoring for this research study)

- Review 100% of all informed consent forms
- Review 100% of subject eligibility.
- Review 100% of CRF depending on the sample size.

Scope of Monitoring (Monitors Responsibilities)

The Monitor's primary responsibilities (GCP 5.18.4), when relevant to the clinical trial/research study, are to:

- 1- Verify that the Investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, i.e., facilities including laboratories, equipment and staff are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- 2- Verify that investigational product(s):

- i) Storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
 - ii) Are supplied only to subjects eligible to receive investigational product(s) and at the protocol-specified dose(s).
 - iii) Are provided with necessary instruction on proper usage, handling, storage, and returns process.
 - iv) Receipts, use and return at the trial sites are controlled and documented adequately.
 - v) Disposition (if unused) at the trial sites complies with applicable regulatory requirement(s), and in accordance with the sponsor.
- 3- Verify that the Investigator follows the approved protocol and all approved amendment(s), if any.
- 4- Verify that written informed consent has been obtained before each subject's trial participation.
- 5- Ensure that the Investigator receives the current Investigator's Brochure, all documents, and all trial supplies required to conduct the trial properly and to comply with applicable regulatory requirement(s).
- 6- Ensure that the Investigator and their trial staff are qualified to conduct the study and fully trained in the protocol.
- 7- Verify that the Investigator and their trial staff are performing the specified trial functions in accordance with protocol and any other written agreement between the sponsor and the Investigator/institution and have not delegated these functions to unauthorized individuals.
- 8- Verify that the Investigator is enrolling eligible subjects only.
- 9- Report the subject recruitment rate.
- 10- Verify that source documents and other trial records are accurate, complete and maintained.
- 11- Verify that the Investigator provides all required reports, notifications, applications and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- 12- Check the accuracy and completeness of CRF entries, source documents and other trial-related records against each other. The Monitor should specifically verify that:
 - i) Data required by protocol is reported accurately on the CRFs and is consistent with source documents.
 - ii) The IMP has been administered in accordance with the protocol and any deviation has been reported to the sponsor in an appropriate manner.
 - iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with protocol on the CRFs.
 - iv) Visits that subjects fail to attend, tests not conducted, and examinations not performed, are clearly reported as such on the CRFs and captured as protocol deviations.
 - v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

- 13- Determine whether all adverse events (AEs) are appropriately reported within the time periods required by GCP guidelines, protocol, the IRB/IEC, the sponsor and applicable regulatory requirement(s).
- 14- Determine whether the Investigator is maintaining essential documents (see ICH E6 section 8. Essential Documents for the Conduct of a Clinical Trial).
- 15- Inform the Investigator of any CRF entry error, omission, or illegibility. The Monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the Investigator or a member of their trial staff authorized to initial CRF changes on behalf of the Investigator. This authorization should be documented.
- 16- Communicate deviations from protocol, SOPs, GCP guidelines, and applicable regulatory requirements to the Investigator, taking any appropriate action designed to prevent recurrence.

Study Files

(Indicate who will be responsible for monitoring the contents of study files and how often this will occur in order to ensure they are up to date)

Specify the type and nature of study files to be monitored, for example:

Protocol:

- Signed protocol
- Protocol amendments.

IRB:

- IRB protocol, CRF, Informed consent....etc approvals
- Serious Adverse Event reports to the IRB.

The Trial Master File including these documents will be kept in the site, any electronic data will be stored in KAIMRC server.

Study Documentation

Verify all applicable documents are completed and maintained by the PI. The following are examples of essential documents that must be reviewed by the Monitoring Unit:

- IRB, FDA, and other regulatory documents (e.g. reports, correspondence)
- Signed Protocol
- Investigator Brochure
- Consent Form and IRB-approved information for subjects
- CRF's
- Investigator and Sub-Investigators CV or documentation of qualifications and training
- Site Signature Log/Delegation of Responsibility Log

- Lab Normal Ranges
- Lab Certifications
- Screening Log
- Enrollment Log
- Adverse Event Reports
- Adverse Event Log
- Correspondence
- Subject Code List
- Product Accountability Log (IDS Registry)
- Product Handling and Storage Instructions
- Product Shipping Records and Certificates of Analysis
- Record of Retained Samples
- Decoding Procedures for Blinded Trials
- Record Retention Plan.

For Electronic Data, the monitors will have their own access to OpenaClinica.

Monitor-Investigator Meeting

At the end of each monitoring visit, the Monitor will meet with the PI or Research Coordinator to discuss any findings.

Documentation of Findings

The Monitoring Unit will send a copy of the Monitoring Report to the Head of the Research Office, KAIMRC and must send the same report to the PI.

The Monitoring Report will describe the progress of the research study, the findings identified during monitoring visits, unresolved items and follow up requirements. The Monitor conducting the visit will sign and date each Monitoring Report. If major findings are identified during the visit, the signature of the Head of the Research Office is also required on the report.

The Monitoring Report usually contains, but is not limited to the following:

- A list of documents and records reviewed
- Subject accrual rate
- Number of Case Report Forms (CRFs) reviewed
- Assessment of Investigational Product (IP) accountability
- Protocol Compliance Assessment.

(Describe how data queries will be generated and processed by the PI)

Queries examples:

- Missing data
- Incomplete source documents
- Out of window subject visits.

Study Completion

(Describe how study close out procedures will occur)

- All remaining investigational products to be returned to the sponsor
 - Study files and data will be retained by the PI for a period of not less than three (3) years after the marketing approval of the investigational product.
 - Ensure that the PI signs off on any tracking logs that were used during the study.
 - Ensure that the appropriate version of signed and dated Informed Consent Forms is on file for every subject.
 - Check that all source data is complete (all lab reports and ECGs have been signed and dated with Clinical Significance assessed by the PI/Sub-I) and that all AEs/SAEs have been signed off by the PI/Sub-I and that they were followed to resolution as specified by the protocol. Finally, check that all significant Protocol Deviations have been properly recorded and the sponsor/IRB has been notified as appropriate.
 - Remind the PI his/her responsibilities including: query/data collection following the close-out visit, essential document retention, publication rights, etc.
 - Write a study completion report and send to PI and Research Office.
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